IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#9
B. White
10-25-93

Applicant: Malcolm J. Simons

Assignee: GeneType AG

Title: "INTRON SEQUENCE ANALYSIS METHOD FOR DETECTION OF ADJACENT AND REMOTE LOCUS ALLELES AS HAPLOTYPES"



Serial No. 07/949,652 Filed: September 23, 1992

Examiner: unknown Group Art Unit: 1807

Attorney Docket No.: M-1647-6C

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THE COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

DECLARATION

Sir:

I, Leroy Hood, hereby declare the following. I am Gates Professor and Chairman, Department of Molecular Biology of the University of Washington School of Medicine, Seattle, Washington. Attached is a copy of my curriculum vitae.

I have reviewed data provided by Malcolm Simons related to his discovery that one could use relatively short regions of non-coding sequences, on the order of one to two kilobasepairs, to define the corresponding coding region allele. Malcolm Simons data related to HLA genes. The data demonstrated that relatively short non-coding region sequences contained informative polymorphisms which can be used as the basis of an HLA typing system. I have also seen the Declaration by Peter Gresshoff stating that he has observed similar informative polymorphisms in an intergenic region near the nitrogen tolerant symbiosis (NTS) gene in soybeans which polymorphisms were indicative of the co-cultivar.

In my research, I sequenced a 100 kilobase region of the Alpha Delta T-cell receptor gene in both mouse and man. The T-cell receptor genes are a paradigm of the diversity genes.

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In particular, the gene undergoes somatic cell rearrangements to provide the required repertoire of binding regions of the T-cell receptor protein. Therefore, I did not expect to find a high level of homology between the mouse and human sequences. However, the homology between mouse and man is approximately 70%. That is approximately the homology many coding regions between mouse and man exhibit. Yet 95% of the sequenced region was non-coding. This observation was a great surprise to me.

Malcolm Simons' data demonstrates that the percentage of homology of non-coding regions and of coding regions in different alleles of the HLA loci is approximately the same. My data demonstrated a similar phenomenon between genes of species which diverged approximately seventy to eighty million years ago. This phenomenon is particularly striking in the T-cell receptor gene which is a paradigm of the diversity genes.

The HLA data and the NTS data indicate the presence of informative polymorphisms in non-coding regions in these vastly different types of genes from species that diverged tens of millions of years ago. In addition, the type of homology I found in sequencing non-coding regions of mouse and man in the Alpha Delta T-cell receptor is consistent with these findings. Therefore, I believe that informative polymorphisms which are indicative of linked alleles and haplotypes are present throughout the eukaryotic genome.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 7/7/93

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7/20/93

# CURRICULUM VITAE

**Name:** Leroy E. Hood

**Date and Place of Birth:** Missoula, Montana - October 1938

**Citizenship:** United States

**Marital Status:** Married 1963 - two children

**Education:**

| | |
|---|---|
| 1960 - B.S. | California Institute of Technology |
| 1964 - M.D. | The Johns Hopkins School of Medicine |
| 1968 - Ph.D. | California Institute of Technology - Immunoglobulins: Structure, Genetics, and Evolution |

**Brief Chronology of Employment:**

| | |
|---|---|
| 1963 - 1964 | NIH Predoctoral Fellowship, California Institute of Technology |
| 1964 - 1967 | NIH Postdoctoral Fellowship, California Institute of Technology |
| 1967 - 1970 | Senior Investigator, Immunology Branch, GL&C, NCI, National Institutes of Health, Bethesda, MD |
| 1970 - 1973 | Assistant Professor of Biology, California Institute of Technology |
| 1973 - 1975 | Associate Professor of Biology, California Institute of Technology |
| 1975 - 1977 | Professor of Biology, California Institute of Technology |
| 1977 - 1992 | Bowles Professor of Biology, California Institute of Technology |
| 1980 - 1989 | Chairman, Division of Biology, California Institute of Technology |
| 1981 - present | Director, Cancer Center, California Institute of Technology |
| 1989 - 1992 | Director, NSF Science and Technology Center for Molecular Biotechnology, California Institute of Technology |
| 1992-present | William Gates III Professor and Chairman, Dept. of Molecular Biotechnology, School of Medicine, University of Washington |

**Academic and Professional Honors:**

Hinrichs Memorial Award - Caltech 1960 - Outstanding student leader
B.S. with Honors - Caltech 1960
Alpha Omega Alpha - Johns Hopkins Medical School 1963
NIH Career Development Award - 1971-1976
Camille and Henry Dreyfus Teacher-Scholar Grant - 1974
Endowed Professorship - The Ethel Wilson Bowles and Robert Bowles Professor of Biology, 1977
Howard Taylor Ricketts Medal - University of Chicago - Outstanding accomplishment in the medical sciences, 1980
Bridges Award - ARCS Foundation - Communication of science to the general public, 1981
Harvey Lecturer - The Rockefeller University, 1982
National Academy of Sciences, 1982
American Academy of Arts and Sciences, 1982
Jesup Lecturer (Molecular Evolution) - Columbia University, 1983
3M Life Sciences Award - Significant contributions to the health and welfare of mankind, 1984
The Ernst W. Bertner Memorial Award - The University of Texas System Cancer Center, University of Texas at Houston, 1985

**Academic and Professional Honors continued:**

California Scientist of the Year, 1985
One of the Science Digest's 100 Top Innovators - For the development of highly sophisticated instruments for the synthesis and analysis of genes and proteins, 1985
Analytical Prize, German Society for Clinical Chemistry Award for "the development of microchemical facilities for high-sensitivity protein sequencing," 1986
Doctor of Science honorary degree, Montana State University, Bozeman, Montana, 1986
Louis Pasteur Award for Medical Innovation for "studies that bring new perceptions of nature and impact medicine in the future," 1987
Fellow of the American Association for the Advancement of Science for "studies in molecular immunology and the development of techniques in protein and nucleic acid chemistry," 1987
ARCS' Man of Science for pioneering research in "deciphering the message of DNA," 1987
Isco Award for Significant Contributions to the Field of Biochemical Instrumentation, University of Nebraska-Lincoln, 1987
Doctor of Science honorary degree, Mt. Sinai School of Medicine of the City University of New York, 1987
Dickson Prize in Medicine for contributions to immunology and molecular biology, 1987
Albert Lasker Basic Medical Research Award for studies of immune diversity, 1987
Distinguished Service Award of The 1988 Miami BIO/TECHNOLOGY Winter Symposium for pioneering the automation of protein and DNA sequencing and synthesis, 1988
Doctor of Science honorary degree, University of British Columbia, Vancouver, BC, 1988
Rabbi Shai Shacknai Memorial Prize in Immunology and Cancer Research, Hebrew University, 1988
Commonwealth Award of Distinguished Service for work in developing instruments used to study modern biology and medicine, 1989
Doctor of Science honorary degree, University of Southern California, Los Angeles, California, 1989
The Cetus Award for Biotechnology - ASM 1989
Steven C. Beering Award, Indiana University School of Medicine, 1989
Doctor of Humane Letters honorary degree, Johns Hopkins University, Baltimore, MD, 1990
American College of Physicians Award - For distinguished contributions in science as related to medicine, 1990
Franz Groedel Medal, American College of Cardiology, 1991
Fellow of the International Institute of Biotechnology, Canterbury, Kent, UK, 1992
Fifth Annual Duke University Award for Immunologic Research, 1992
Doctor of Science Honorary Degree, Wesleyan University, 1992

**Membership in Professional Organizations:**

Sigma Xi
American Association for the Advancement of Science
American Association of Immunologists
American Society for Clinical Investigation
American Society of Biological Chemists
American Society of Zoologists

**Lectureships:**

Welch Foundation Conference on Chemical Research - Houston, 1974
Distinguished Lectureship - Department of Zoology, University of Texas-Austin, 1977
Mary Huling Edens Lecturer in Medical Genetics - Galveston, 1979
Philips Lecturer - Haverford, 1980
Howard Taylor Ricketts Lecturer - University of Chicago, 1980
Camille and Henry Dreyfus Lecturer - Pomona College, 1980
Kinyoun Lecturer - National Institutes of Health, 1980
Smith Kline and French Lecturer - Vanderbilt University, 1980
Dan Campbell Lecturer - Asilomar, 1981
Michael Heidelberger Lecturer - Columbia University, 1981
Shaffer Lecturer - Washington University School of Medicine, 1981
Watkins Lecturer - Wichita State University, 1981
Stanhope Bayne-Jones Memorial Lecturer - Johns Hopkins Medical School, 1981
Wellcome Burroughs Lecturer - Mt. Sinai Medical School, 1981
Jesse Beams Memorial Lecturer - University of Virginia Medical School, 1981
Robert W. Woodruff Lecturer - Emory University, 1981
John M. Chemerda Lecturer - The Pennsylvania State University, 1982
Marrs McLean Lecturer - Baylor College of Medicine, 1982
Carter-Wallace Lecturer - Princeton University, 1982
Smith-Kline Lecturer - Philadelphia, 1982
Sommer Memorial Lecturer - Portland, 1982
Dreyfus Distinguished Lecturer - Indiana University, 1982
Visiting Professor of Biochemistry - University of California, Riverside, 1982
Dreyfus Distinguished Lecturer - St. Olaf College, 1982
Linus Pauling Lecturer - Stanford University, 1983
Wendell Griffith Lecturer - St. Louis University, 1983
Syme Lecturer - Walter and Eliza Hall Institute of Medical Research, Melbourne, 1983
Allied Lecturer - Rutgers University, 1983
Smith Kline and French Lecturer - Univ of California, San Francisco, Medical School, 1983
Benjamin Knox Rachford Memorial Lecturer - Univ of Cincinnati College of Medicine, 1983
Belfort Lecturer - Purdue University, 1983
Stuart Memorial Lecturer - Brown University, 1983
Charles Heidelberger Memorial Lecturer - University of Southern California, 1984
Albert Coons Memorial Lecturer - Harvard Medical School, 1984
Nellie Fox Distinguished Lecturer - Northwestern Medical School, 1984
President's Lecturer - Texas A&M, 1984
J. S. Blumenthal Lecturer - University of Minnesota, 1986
Wellcome Visiting Professor - University of Michigan, 1986
Barton Lecture - University of Oklahoma, 1986
Maurice Ogur Memorial Lecture, Southern Illinois University at Carbondale, 1986
Nieuwland Lecturer in Biological Sciences, the University of Notre Dame, 1986
R. E. Dyer Lecturer, Bethesda, Maryland, 1986
Rennebohm Lecturer - University of Wisconsin, Madison, 1987
The Committee of the Interscience Conference on Antimicrobial Agents and Chemotherapy Lecturer, New York, 1987
Albert M. Snell Memorial Lecturer - Research Institute, Palo Alto Medical Foundation, 1987
The 1987 Benedum Lectures - West Virginia University, 1987
Herman Beerman Lecturer - The Society for Investigative Dermatology, 1987
Rabbi Shai Shacknai Memorial Prize Lecturship, Hebrew University, 1988
James M. Craig Memorial Lecture - Oregon State University, 1988
Wayne State University Distinguished Lecturer for the Center of Molecular Biology, 1989

**Lectureships continued:**

H. Willard Davis Lecture - The University of South Carolina, 1989
The Cape Lecture - McGill University, 1989
Jeanette Oshman Efron Lecture in Molecular Genetics - Baylor College of Medicine, 1989
Myron Karon Lecturer - Childrens Hospital of Los Angeles, 1989
Los Angeles Society of Pathologists Lecture, Los Angeles, 1989
Visiting Scholar, National Institute of Dental Research, NIH, 1990
John G. Reinhold Lecturer, University of Pennsylvania, 1990
Bristol Myers Lecture, University of Colorado, Boulder, 1990
Hobart H. Willard Lectureship in Analytical Chemistry - University of Michigan Medical School, 1990
Roy and Eva Hong Lectureship in Molecular Biology - University of Illinois, 1990
Jeanette Piperno Memorial Lectureship - Temple University, 1990
Microbiology Graduate Students Distinguished Lecturer - Iowa State University, 1990
Basil Staples Visiting Professorship - University of Maine, 1990
Bren Fellows Lectureship - University of California, Irvine, 1990
Leo S. Weil Memorial Lecturer, Touro Infirmary - Tulane Medical Center and Louisiana State University Medical Center, New Orleans, 1991
Jessie & John Danz Lectureship - University of Washington, 1991
Kosuge Memorial Lectureship - University of California, Davis, 1991
Franz Groedel Lecture, Opening Plenary Session, American College of Cardiology, 1991
Hoffman-LaRoche Lectureship in Microbiology - the Waksman Institute, Rutgers University, 1991
The Aser Rothstein Lecture - Research Institute of the Hospital for Sick Children, Toronto, Canada, 1991
Distinguished Medical Scientist Lectureship - Ohio State University, 1991
Richard S. Polacsek Lecture, Welch Medical Library - The Johns Hopkins University, 1991
William Weigle Memorial Lecture - Scripps Research Institute, 1992
Hooke Lecture, XVI Congress of the International Society for Analytical Cytology, 1993
Serono Lecture, American Society of Andrology, 1993

**Editorial and Advisory Duties:**

Associate Editor: *Journal of Immunology*, 1970-1975
Advisory Editor: *Immunochemistry*, 1970-1975
Editorial Advisory Board: *Biochemistry*, 1975-1981
Advisory Board: *Biochemical Genetics*, 1975-present
Editorial Board: *Biological Regulation and Control: A Comprehensive Treatise* (Plenum), 1975-present
Associate Editor: *Cell*, 1981-1985
Editorial Board: *Journal of Molecular Evolution*, 1981-present
Scientific Advisory Board: Cleveland Clinic, 1985
Editorial Board: Proteins: *Structure, Function and Genetics*, 1986
Scientific Advisory Committee: Department of Medicine at the Univ. of Alabama, 1987
Advisory Board: *Clinical Immunology and Immunopathology*, 1987
Scientific Advisory Committee: Cancer Center at the University of Chicago, 1987-1992
Editorial Board: *Genomics*, 1988-present
Editorial Board: *Biotechniques*, 1988-present
Editorial Board: Genetic Analysis and Applications, 1990-present
Board of Scientific Advisors: Jane Coffin Childs Memorial Fund, 1990-present
Science Advisory Board: Discovery Museum of Orange County, 1990-present.
Scientific Advisory Board for Biological Sciences: Molecular Simulations, Incorporated, 1990-present.
Editorial Board: *Current Opinion in Biotechnology*, 1990-present.

**Editorial and Advisory Duties:**

Advisory Board: Network of Centres of Excellence, University of British Columbia, 1990-present.
Editorial Board: Molecular Phylogenetics and Evolution, 1991.
Advisory Board: Human Genome Center, Lawrence Berkeley Laboratory, 1991-present
Editorial Broad: *Human Mutation*, 1991-present.
Scientific Advisory Board: Roche Molecular Systems, 1992-present

**Appointments:**

Special Grants Committee, American Cancer Society, California Division, 1973-1977
Chairman, Special Grants Committee, American Cancer Society, California Division, 1975-1977
Study Section of Human Biology Program, National Science Foundation, 1972-1976
Chairman of FASEB Conference on Genetics and Biological Evolution, 1975
Genetics Study Section, National Institutes of Health, 1979-1981
Visiting Committee for the Department of Biology, MIT, 1979-present
Committee to select California Scientist of the Year, 1980
Scientific Advisory Board for Max-Planck-Institut für Experimental Medizin at Göttingen, 1980-present
Chairman, Committee to select California Scientist of the Year, 1981
Visiting Committee for Cellular and Developmental Biology, Harvard University, 1982-present
External Advisory Committee of the USC Comprehensive Cancer Center, 1987-present
Genome Advisory Committee: NIH, 1989-1992
Genome Advisory Committee: DOE, 1989-present
Commisssion on Life Sciences: National Academy of Sciences, 1989-present
Executive Committee, Human Genome Organization, 1989-present
California Council on Science and Technology, 1989-present
Board of Directors, Sigma Xi, 1991-present
The Canadian Genetic Disease Network, Board of Directors, 1991-present
Board of Directors, The Seaver Institute, 1992-present

**Research Interests:**

Genetics and Evolution of Multigene Systems
Genetics and Evolution of Antibody Diversity
Organization of Antibody and MHC Genes
Chemistry and Genetics of Eukaryotic Membrane Proteins
Protein Evolution
Protein Chemistry and Immunochemistry
Microchemical Instrumentation

**Nonscientific Interests:**

Mountaineering and climbing
Running
Photography
Science fiction

## BIBLIOGRAPHY

### A. Books


1. Wood, W. B., J. Wilson, R. Benbow and L. Hood. **Biochemistry: A Problems Approach**. 1st Edition. W. A. Benjamin, Inc., Menlo Park, CA, 1974; 2nd Edition, 1981.
2. Hood, L., J. Wilson and W. B. Wood. **Molecular Biology of Eucaryotic Cells**. W. A. Benjamin, Inc., Menlo Park, CA, 1975.
3. Hood, L., I. Weissman and W. B. Wood. **Immunology**. W. A. Benjamin, Inc., Menlo Park, CA, 1978.
4. Weissman, I., L. Hood and W. B. Wood. **Essential Concepts in Immunology**. W. A. Benjamin, Inc., Menlo Park, CA, 1978.
5. Hood, L. E., Weissman, I. L., Wood, W. B. and Wilson, J. H. **Immunology**. Benjamin/Cummings, Menlo Park, CA, 2nd Edition, 1984.
6. Hood, L. Biology and Medicine in the Twenty-First Century. **In: The Code of Codes,Scientific and Social Issues in the Human Genome Project.** Eds.Kevles, D. J. and L. Hood. Harvard University Press, Cambridge, MA, 1992.


### B. Patents


1. Hood, L. E. and M. W. Hunkapiller. Apparatus for the performance of chemical processes. U.S. Patent No. 4,252,769, February 24, 1981.
2. Hood, L. E., M. W. Hunkapiller, W. J. Dreyer, R. M. Hewick and A. W. Stark. Improved apparatus and method for the sequential performance of chemical processes. Filed September 23, 1980 with U.S. Patent Office.
3. Hood, L. E., I. L. Weissman and M. S. McGrath. Diagnostic reagents based on unique sequences within the variable region of the T-cell receptor and uses thereof. U.S. Patent No. 4,886,743, December 12, 1989.


### C. Research Papers


1. Bennett, J. C., L. Hood and W. J. Dreyer. Evidence for amino acid sequence differences among proteins resembling the L-chain subunits of immunoglobulins. *J. Mol. Biol.* **12**, 81-87, 1965.
2. Hood, L. E., W. R. Gray and W. J. Dreyer. On the mechanism of antibody synthesis: A species comparison of L-chains. *Proc. Natl. Acad. Sci. USA* **55**, 826-832, 1966.
3. Hood, L., W. R. Gray and W. J. Dreyer. On the evolution of antibody light chains. *J. Mol. Biol.* **22**, 179-182, 1966.
4. Gray, W. R., W. J. Dreyer and L. Hood. Mechanism of antibody synthesis: Size differences between mouse kappa chains. *Science* **155**, 465-467, 1967.
5. Hood, L., W. R. Gray, B. G. Sanders and W. J. Dreyer. Light chain evolution. *Cold Spring Harbor Symp. Quant. Biol.* **32**, 133-146, 1967.
6. Dreyer, W. J., W. R. Gray and L. Hood. The genetic, molecular, and cellular basis of antibody formation: Some facts and a unifying hypothesis. *Cold Spring Harbor Symp. Quant. Biol.* **32**, 353-367, 1967.
7. Howell, J. W., L. Hood and B. G. Sanders. Comparative analysis of the IgG heavy chain carbohydrate peptide. *J. Mol. Biol.* **30**, 555-558, 1967.
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11. Grant, J. A., M. E. Lamm and L. Hood. N-terminal sequence heterogeneity of guinea pig anti-DNA kappa chains. *Immunochemistry* **6**, 645-648, 1969.
12. Hood, L., H. Lackland, K. Eichmann, T. J. Kindt, D. G. Braun and R. M. Krause. Amino acid sequence restriction in rabbit antibody light chains. *Proc. Natl. Acad. Sci. USA* 63, 890-896, 1969.
13. Eichmann, K., K. Lackland, L. Hood and R. M. Krause. Induction of rabbit antibody and molecular uniformity after immunization with group C streptococci. *J. Exp. Med.* **131**, 207-221, 1970.
14. Hood, L., J. A. Grant and H. C. Sox, Jr. On the structure of normal light chains from mammals and birds: Evolutionary and genetic implications. In: *Developmental Aspects of Antibody Formation and Structure*, **I**, 283-309, 1970.
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16. Sox, H. C. and L. Hood. Attachment of carbohydrate to the variable region of myeloma immunoglobulin light chains. *Proc. Natl. Acad. Sci. USA* **66**, 975-982, 1970.
17. Hood, L., M. Potter and D. McKean. Immunoglobulin structure: Amino terminal sequences of kappa chains from genetically similar mice (BALB/c). *Science* **170**, 1207-1210, 1970.
18. Hood, L., K. Eichmann, H. Lackland, R. Krause and J. J. Ohms. Rabbit antibody light chains and gene evolution. *Nature* **228**, 1040-1044, 1970.
19. Sanders, B. G. and L. Hood. Antigenic properties and electrophoretic heterogeneity of polypeptide chains from IgG immunoglobulins. In: *Studies in Genetics*, Vol. VI, 29-47. Ed. M. R. Wheeler. University of Texas Press, Austin, Texas, 1971.
20. Grant, J. A. and L. Hood. N-terminal analysis of normal immunoglobulin light chains. I. A study of thirteen individual humans. *Immunochemistry* **8**, 63-79, 1971.
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22. Grant, J. A., B. Sanders and L. Hood. Partial amino acid sequences of chicken and turkey immunoglobulin light chains. Homology with mammalian λ chains. *Biochemistry* **10**, 3123-3132, 1971.
23. Waterfield, M. D., J. W. Prahl, L. E. Hood, T. J. Kindt and R. M. Krause. Restricted structural heterogeneity in antibodies: Might different heavy chains have a common light chain? *Nature New Biol.* **240**, 215-217, 1972.
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26. McKean, D., M. Potter and L. Hood. Mouse immunoglobulin chains. Partial amino acid sequence of a κ chain. *Biochemistry* **12**, 749-759, 1973.
27. McKean, D., M. Potter and L. Hood. Mouse immunoglobulin chains. Pattern of sequence variation among κ chains with limited sequence differences. *Biochemistry* **12**, 760-771, 1973.
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# RESTRICTION FRAGMENT LENGTH POLYMORPHISM OF HLA GENES: SUMMARY OF THE 10TH INTERNATIONAL WORKSHOP SOUTHERN BLOT ANALYSIS

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# RESTRICTION FRAGMENT LENGTH POLYMORPHISM OF HLA GENES: SUMMARY OF THE 10TH INTERNATIONAL WORKSHOP SOUTHERN BLOT ANALYSIS

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## I. SUMMARY

The 10IW represented the first international effort to evaluate the role of Southern blot technology in characterization of loci and haplotypes comprising the HLA system. The data generated from the use of 12 restriction endonucleases on DNA from 70 of the 107 cells was technically valid as revealed by fragment pattern consistency of hidden duplicates, and by fragment pattern relations with known specificities and haplotypes. The review details the total data, comprising more than 1,100 fragments associated with 11 probes.

From a practical standpoint, the Southern blot technique has been shown to be suitable for HLA typing of class II locus genes. One hundred eighty-seven 'unique' fragments were identified using DRB, DQA and DQB probes. While RFLP 'unique' fragments correlating with individual HLA specificities were not detected for all HLA class II antigens, the presence or absence of fragments correlating with >2 specificities provided the basis for comprehensive HLA class II DNA typing.

DNA typing using the DPA and DPB locus probes has revealed RFLP patterns which correlate closely with known DPw1-DPw5 specificities. Two corresponded to the nucleotide sequence subtypes DPB2.2 and DPB4.2 (Simons and Erlich, this volume), while 7 associated with DPB New sequence variants in cells lacking assigned DPw specificities.

For class I, 46 'unique' fragments were identified. The achievement of allele and haplotype discriminatory RFLP patterns might not have been expected, since DNA typing for HLA A, B and C alleles typing was performed using only a class-specific probe, and not locus-specific probes. However, as for class II, the combination of these 'unique' fragments, together with the presence or absence of multi-specific fragments, did enable the different haplotypes to be distinguished. A new finding was the identification of 22 fragments correlating with C locus specificities, including RFLPs which are present only within the C locus blank. It had been previously known that A locus genes correlated with 'unique' fragments. Similarly, it was known that 'unique' fragments only existed for a limited number of the B locus specificities, using the commonly employed restriction endonucleases of the 10IW. The known high degree of linkage disequilibrium between the three sero-expressed loci, and presumably also involving others of the class I loci, offset the paucity of B locus 'unique' fragments, and enabled class I

locus A and C types, and A, B and C haplotypes, to be identified.

More comprehensive information than previously existed was obtained on loci that are less relevant to the practice of HLA typing. However, RFLP patterns arising from non-expressed polymorphic loci (eg. DQA2, DQB2, DOB, DNA, DPA2, DPB2) contribute valuable information towards understanding the evolutionary relationships between haplotypes and their component loci. Tree dendogram analysis provides an indication of evolutionary relationships between the haplotypes of the cells studied in the 10IW.

This report is a comprehensive presentation of the total RFLP data on the reference panel cells. The figures and tables are presented in a manner which allows for ready inspection of the total database, and for further individual analysis. All data contributed by the workshop standardization centers, and all interpretations of the data as described in the DNA locus probe reports, have been considered. This review should be read in conjunction with these component reports. It should be noted, however, that it has been necessary to revise the interpretation of some reports in view of central data analyses additional to those available to the rapporteurs.

## II. INTRODUCTION

HLA gene restriction fragment length polymorphisms (RFLP) have been systematically examined using standardized Southern blot protocol (1). This workshop represents the first international multi-laboratory effort towards the ultimate goal of single locus allele, and multi-locus haplotype, characterization at the DNA level. The results reported here should be viewed as an attempt to evaluate the role of Southern blot technology in characterization of the loci comprising the HLA system. This chapter provides an overview of the patterns associated with over 1,100 fragments resulting from the use of up to 12 restriction endonucleases on DNA from 70 of the 107 10IW reference panel cells.

The design and execution of the Southern blot component of the workshop has been described elsewhere in this volume (2). In this report the RFLP data is presented in a manner which is both comprehensible on inspection and amenable to further analysis. It takes into account information contributed by the working groups as reported in these Proceedings, and should be read in conjunction with the individual reports.

The main criterion for inclusion of cells in the 10IW was homozygosity for DR and DQ specificities. Representation of Dw specificities was also a consideration. Additional cells were included which were suspected or known to be variants of

the main types. As a result, some specificities were not included (e.g. DRw10), while some were present in only one cell (e.g. Dw20, Dw21, DB6, Dw13, Dw10). In the Southern blot component, 70 of the total 107 cells were studied.

In the final phase of data analysis, all cells were reassessed on the basis of serological reactivity, and HLA types reassigned. Two cells (9104, 9107) were not serologically typed by the 10IW core serology serum set and therefore were dropped from analysis. Only one each of the duplicated cells (9032, 9056) was retained. Thus, RFLP analysis is based on 68 cells and 136 haplotypes.

Although RFLP analysis by Southern blotting is a direct approach to gene detection, it is usually only an indirect method of identifying gene sequence variation. Restriction sites do occur within exons, but the large majority of RFLP sites for the restriction endonucleases employed in 10IW occur in non-exon regions. Thus, the relationship between exon sequence variation and RFLP is a function of linkage disequilibrium between intron and flanking region fragments bearing polymorphic restriction sites, and exon segments with allelic variability. Careful selection of restriction enzyme/HLA locus probe combinations is critical to the identification of allelic differences.

Unlike serology, there are no 'blank' alleles in Southern blot analysis. All fragments generated by a particular endonuclease can be expected to be present in the corresponding Southern blot lane. Furthermore, intensity of detectable fragments provides information on gene dosage.

It is often stated that the disadvantage of RFLP for HLA typing is that polymorphic restriction sites are predominantly located outside of the exons encoding allelic variation. The argument contends that HLA typing should be directed at the exon sequences themselves or at expressed products of the genes. The former approach requires nucleotide sequence information on all relevant exons. While most allelic variation is encoded in the first domain exon, the possibility of a role for second domain sequences is suspected, and cannot be eliminated in the interpretation of allele specific typing limited to first domain analysis. In principal, HLA typing technologies based upon the detection of gene sequence-translated products will be the final arbiters of exon involvement. As reported elsewhere, this workshop has advanced our understanding of HLA class II alpha and beta chain structural polymorphism (3). However, from a technological viewpoint, 2-D gel electrophoresis is not likely to be reduced to a routine procedure for HLA typing, and resolution of sequence-similar chains can be difficult. Epitope detection by T-cell cytotoxicity and proliferative

procedures have proved to be highly discriminatory (4), but are not yet realistic procedures for routine HLA typing.

The results reviewed here establish that serologically or cellularly detectable differences between HLA specificities are associated with discriminatory RFLP patterns based on the presence or absence of sites for restriction endonuclease cleavage. The results indicate that the fragments generated by combinations of twelve enzymes used in the workshop, and even by single enzymes, detect differences between cells that have not been distinguished by serological typing of the gene products. In addition to detection of differences within loci, cluster analysis of fragments generated at separate loci reveals patterns of linkage disequilibrium within HLA haplotypes. Thus, involvement of extended lengths of the haplotype through hybridization with full length locus probes in RFLP typing provides for distinction between cells whose exon products may not be easily distinguishable. The apparent disadvantage of non-exon polymorphism detection by RFLP is, in fact, an asset in both individual locus-allele, and multi-locus haplotype, characterization.

Fragment patterns associated with each cell have been investigated principally by cluster analysis involving assessment of successive pairs of cells for fragment pattern similarity. In this review, cell fragment pattern

relationships have been presented as Tree dendograms. By utilizing all fragment information, Tree analysis reveals haplotype relationships which, in turn, can be presumed to reflect the evolutionary development of differences between the haplotypes. Thus, RFLP analysis provides comprehensive locus and haplotype identification based on the evolutionary development of haplotype differences.

One outcome of the locus and haplotype resolving power of RFLP is that differences have been identified between cells to which the same HLA specificities have been assigned. When the entire gamut of gene products, detectable as polypeptide chains or as epitopes detectable by serological or cellular reagents, is established, and when exon nucleotide sequence analysis only infrequently detects new allelic varieties, it will again be necessary to reassess RFLP fragment patterns to determine the relationship between RFLP and 'definitive' HLA haplotypes. The data has been presented in a manner which facilitates this future event. Unlike serology, in which many of the reagents, and the results obtained using those reagents, vary from workshop to workshop, the Southern blotting component has generated RFLP patterns that can be expected to be obtained each time the same enzymes and probes are applied to HLA RFLP analysis of the same cells. The sizes assigned to fragments may differ slightly, but the pattern

relationships between fragments can be expected to be constant.

This report is divided into sections corresponding to the usual HLA classes and regions, namely class I, class III, class II alpha sub-regions and beta sub-regions. Virtually all fragment data is presented in the figures. The raw clustering outputs have been edited by rearranging the row sequence of listed cells and the column sequence of contiguous fragments in order both to simplify the complexity of pattern clusters, and to produce an output in the form familiar to HLA serologists.

## III. RESULTS

Since the format for presenting the results for each individual locus, and for combinations of loci, is similar, it may be helpful to detail the approach taken using a representative locus. The DOB locus is suitable for this purpose.

### 1. Class II DOB locus

Figs. 1-5 reveal the essential results. Fig. 1 shows the pattern resulting from fragment-by-fragment cluster analysis. It can be seen that there are three clusters involving four or more fragments, and an additional five clusters, each comprising two fragments. Six of the total of 30 fragments

generated by the 12 restriction endonucleases and detected using the DOB locus probe show reactivity patterns distinct from all the other fragments.

Two types of information can be obtained from the negative cluster analysis shown in Fig. 2. Firstly, the number of fragments associated with some cells is obviously different from that associated with other cells. Specifically, cells 9005, 9011, 9017, 9018 and 9037 are candidate heterozygotes. Similarly, but less obviously, cells 9007, 9056, 9106, 9028, 9069 and 9071 have features of heterozygosity. Secondly, allelic fragment pairs can be seen. Some such allelic fragments, e.g. BGL 827 and BAM 509; EC1 1285 and MSP 142; MSP 462 and MSP 364; are complete for all 68 cells. Others, (BAM 729 and SST 410; SST 294 and BGL 770) are incomplete in that some cells lack both fragments.

Fig. 3 shows the positive cluster analysis of the same 30 fragments. The fragments have been rearranged in order to illustrate the two clusters which characterize the locus. The five cells recognized as candidate heterozygotes from negative clustering are seen to be true heterozygotes in that they have fragments associated with both of the two main clusters.

The cells in Fig. 3 have been listed according to DQw type. Certain observations can be made about the distribution of DQw

types in association with each of the two main clusters. For example, all DQw4 cells, and all DQw5 cells apart from 9005, are associated with the second cluster in the lower half of the figure. Conversely, all but three of the DQw6 cells are associated with the cluster to the top left of the figure. Thus, it can be seen that DOB locus cluster type stratifies DQw types, in turn providing information on evolutionary relationships.

Fig. 4 depicts the Tree analysis of relationships between the cells based on RFLP patterns associated with the presence or absence of the 30 fragments detected by the DOB locus fragments. Before looking in detail at the cell relationships, and at the degree of those relationships as expressed in the similarity index number, the quality of the RFLP data can be assessed by examining the similarity between the two 'hidden' duplicate pairs, namely cells 9032 and 9056. At this locus, and at all other loci, there was 100% concordance between the duplicates, providing confidence both in the quality of Southern blotting technical performance, and in the validity of the computer-assisted transformation of the raw fragment data.

Fig. 4 indicates that other cells have fragment patterns that are not distinguishable. These are also shown by the similarity index number '100'. Subgroups of cells showing

less than complete concordance form the basis of the Tree. The number 9 at the extreme right of the figure indicates that there is virtually no association between the two major groups comprising the two main clusters.

Fig. 5 depicts the positive cluster analysis in which the cells are listed based on the Tree relationship. Comparison of Fig. 5 with Fig. 3 indicates that fragment reactivity in the former is more tightly blocked, confirming that the computer program has been more effective at grouping similar cells than the subjective attempt represented by Fig. 3. The patterns of variation associated with both of the main clusters are more apparent from Fig. 5.

2. Class I HLA A, B, C loci

In conventional HLA typing, it is customary to seek reagents that are 'unique' for individual specificities. The practice of lymphocytotoxic serology evolves by identification of sera which react with one or a limited number of defined specificities. Similarly, RFLP fragments can be identified which are 'unique' for serological specificities. Other fragments are generated by cells having one or more of the specificities within the group, and are comparable to the useful multi-specific sera. With time, serologists identify reagents with specificities that progressively approach monoreactivity. With sequence information now becoming

available for the class I polymorphic loci, and with the advent of locus-specific probes, it should be possible to achieve a comparable situation whereby fragments occurring in linkage disequilibrium only with a particular haplotype can be supplemented with 'unique' monospecific fragments arising from the use of endonucleases whose restriction sites involve the sequence differences between alleles. This ideal situation already exists for class II analysis, where sequence information is available for alleles of both alpha and beta loci in the three main regions. Sequence information on class I genes is becoming available. For the present, results of the class I RFLP workshop indicate that most allelic differences at the HLA-A and C loci can be detected despite using a class-specific rather than a locus-specific probe.

Two hundred and four (204) fragments were detected by the class I probe using the 11 enzymes. Figs. 6a and 6b show the positive clustering of the total fragments against 68 cells listed by A locus type. Fragments associated with single or limited number serospecificities have been rearranged to illustrate the associations. To the left of the figure, from PVU 480 to PVU 1619, can be seen fragments suitable for detection of HLA-A locus specificities. These are followed by fragments specific for the B locus specificities B8, Bw41, Bw42, Bw44, Bw47, Bw51, Bw57, Bw60 and Bw61 (BAM 2356 to KPN 2644). Then follow 22 fragments associated with C locus

specificities (ECV 1096 to PST 721). Four of these 'specificity-unique' C locus fragments, along with 13 for B locus types and 29 for A locus specificities, are listed in Table 1. Fragments have been included which are present in one additional cell, or absent in one cell stated to bear the relevant specificity. The 22 C locus fragments are examined in more detail in Figs. 7a and 7b, 8 and 9. In Fig. 6b, the remaining fragments are shown to the right of the C locus-associated fragments as two major groups. The first group of thirty-one (31) fragments (PVU 1815 to MSP 217), having reactivity with many cells, showed patterns of co-clustering with individual specificity-associated fragments before the columns were rearranged to simplify recognition of the single specificity fragments. The second group (PVU 1310 to MSP 574) remain in their original position following cluster analysis of the total 204 fragments. Where haplotypes occur two or more times, the distinctive fragment patterns can be readily seen. It is not so obvious that all haplotypes are characterized by distinctive fragment patterns since many of the haplotypes occur in the reference cell panel only once. In fact, all cells distinguishable by serology are also distinguishable by RFLP patterns.

In Figs. 7a and 7b, the C locus-related fragments have been shifted to the first 22 columns (ECV 1096 to PST 721), and the cells rearranged according to C locus type. In Fig. 8,

negative clustering of the C locus-associated fragments reveals the basis for the association. As mentioned earlier, in RFLP each enzyme generates a finite number of fragments. The allelic nature of fragments produced by any one enzyme within a locus results in specificities being positively detectable by the presence of fragments, and confirmed by the absence of allelic fragment(s) for that specificity. Examination of the cell distribution of allelic fragments in Fig. 9 reveals the basis of specificity association. Fragments exist which, in serological terms, would be regarded as 'short' or 'long' in that they are observed in less than all cells of a particular specificity, or they arise in all cells having a particular specificity, plus additional cells. Since these varying degrees of correlation between fragments and exon product-detectable specificities reflects linkage disequilibrium between the restriction site-bearing sequence and the exon sequence, HLA typing by RFLP is based on the empiric identification of those enzymes which happen to generate fragments in linkage disequilibrium with allele-specific sequences. From inspection of Fig. 9, it is apparent that the main HLA C specificities correspond to distinctive RFLP patterns. Sixteen cells listed at the bottom of Fig. 9 lack assigned HLA C specificities. Some of the 16 have RFLP patterns which closely resemble those seen with known HLA C specificities. It should be noted that fragment MSP 427 is present only in the 16 C blank cells, occurring 9 times.

Fig. 10 shows the Tree dendogram analysis of cell relationships according to class I RFLPs. It can be seen that clusters within the Tree reflect HLA haplotypes. Where individual haplotypes occur two or more times, the clustering is obvious, and the clusters involve high similarity indices. Where haplotypes occur only once, the similarity index between adjacent pairs is correspondingly lower. At face value, the clustering patterns suggest a predominant role of the HLA A locus. It should be realized that this reflects the lesser heterogeneity of A locus alleles relative to HLA B locus alleles present in the reference cell panel.

Tree dendogram analysis (Fig. 10) confirms that the combined use of both fragment presence and specificity-associated fragment absence enables cells to be grouped according to established serospecificities, and to be distinguishable where differences exist at the specificity level.

3. Class III loci

A total of 78 fragments are available for analysis using class III locus probes (C2 - 20; C4 - 24; 21OH - 34). Negative cluster of these 78 fragments is shown in Fig. 11. The column-ordering of fragments reveals mutually exclusive fragment pairs for single class III types (e.g. C2: PVU 418, TAQ 491; C2: EC1 676, PST 1165; C2: KPN 988, HID 446. C4: SST 410, TAQ 627; C4: TAQ 707, EC1 750). In the case of the C4

and 21OH loci, interpretation of the existence of mutually exclusive fragment pairs such as BAM 477 and ECV 4563 is uncertain. For class III loci in particular, caution needs to be exercised in the interpretation of pairs of fragments which are mutually exclusive since gene duplications, gene deletions, and the existence of pseudogenes are well established. Only one pair of fragments arises from the same enzyme (C4 HID: 1369; HID 801). These matters are discussed in more detail in the RFLP report for the class III region (5), and in the overview of molecular biology of HLA class III presented in volume II of these proceedings (6).

The negative cluster (Fig. 11) indicates three broad groupings. The upper cells from 9065 to 9105 are relatively restricted in their heterogeneity, and least complex. The second group of cells (9060 to 9059) have significantly increased number of fragments, particularly involving the 21OH loci. The third group of cells (9018 to 9047) have an obvious block absence of fragments in the bottom right corner, while being similar to the cells of the first group for the remainder of the fragment pattern. These latter are known to include cells having deletions in the C4/21OH region (5). This situation is revealed in a more obvious manner by Fig. 12 in which the fragments are positively clustered against the same listing of cells.

Cell relationships involving these three loci are shown as a Tree dendogram in Fig. 13. In Fig. 14, the cells have been regrouped so that those 25 for which C4A and C4B locus types are available are shown at the top of the list. It is apparent that some RFLP patterns group according to C4 phenotype: C4A4, C4B2 - 9066, 9075, 9008; C4A3, C4BQ0 - 9018, 9019, 9020; C4A6, C4B1 - 9052, 9007). Cells typing for C4A3, C4B1 comprise two major RFLP pattern groups (9042, 9065, 9011, 9082; and 9058, 9051, 9048, 9034). Two cells (9105 and 9060) have unique patterns. For C4AQ0, C4B1, the prototype pattern is represented by three cells 9022, 9023, 9088 with the classical HLA haplotype A1, Cw7, B8, while the fourth cell of the group (9050) has a pattern indistinguishable from that of C4A3, C4BQ0 cells. The observed heterogeneity within C4 phenotypes probably reflects the frequent occurrence of gene duplication, gene deletion and other gene rearrangements (6) resulting in the phenomena of contraction and/or expansion within the HLA class III region (7).

## 4. Class II Alpha loci

### 4.1 DRA

There were 17 informative fragments detected by the DRA probe. In Fig. 15, the cluster pattern of these fragments is shown. Negative cluster of these fragments against cells listed by DR type is shown in Fig. 16. Mutually exclusive fragments can be seen involving the three enzymes PVU, TAQ and MSP. It is known from nucleotide sequence analysis of the DRA coding region that the expressed gene is non-polymorphic (8). Thus, the seeming allelism of DRA RFLP fragment patterns must reflect genetic linkage disequilibrium with polymorphic restriction sites in non-coding regions. Nonetheless, these DRA RFLPs do provide useful markers for DNA typing since they correlate strongly with certain DR specificities as shown in Figs. 17 and 18. In Fig. 17, the fragments have been positively clustered against cells listed by DR specificities. From cursory inspection it is obvious that the block fragment patterns relate to DR specificities. The fragments are seen to comprise two main clusters. These patterns are more readily discerned when the cells are sorted according to their Tree relationships (Fig. 18). The less frequent cluster is present in the last 12 cells in the list. These 12 cells comprise all 8 Dw24 cells, 2 of the 3 Dw26 cells, and both DRw8 cells assigned as Dw8.3. Although only six or seven DRA sequences have been determined, this limited number does include haplotypes of both the major RFLP clusters.

## 4.2 DQA

Of the 74 fragments associated with the DQA1 and DQA2 loci, two (KPN 716 and KPN 232) have been excluded. Fig. 19 shows a cluster analysis of the remaining 72 fragments. Negative clustering of these fragments against cells listed by DR type is shown in Fig. 20 in which the 10 cells that are heterozygous for either or both loci have been listed to the bottom of the figure. The last four cells (Nos. 9008, 9007, 9028 and 9106) are heterozygous at the DQA2 locus as revealed by the PVU fragments 819 and 722 (the first two columns) and by the TAQ fragments 209 and 155. Three of these four cells (9007, 9028, 9106) and the remaining six cells (Nos. 9005, 9017, 9018, 9045, 9056 and 9071) are heterozygous at DQA1.

Fig. 21 presents the fragments as positive clusters against cells listed by DQ, Dw and DR specificities. DQA-associated fragments occupy the left two-thirds of the figure (SST 1653 to PST 912). As with the DRA locus, the block patterns of fragment presence and absence are apparent, with greater resolution being achieved with the substantially larger number of DQA fragments. Six TAQ fragments (TAQ 817, 699, 619, 553, 285, 278) are of doubtful validity since they bear no apparent relation to DR or DQ specificities. Fragments reflecting the two major clusters associated with the DQA2 locus are shown at the extreme right of the figure (PVU 819 to MSP 568). Since the DQA2 gene is thought to be non-polymorphic (9), the two

mutually exclusive RFLP patterns presumably reflect polymorphic restriction site(s) in the flanking region.

In Fig. 22, fragments have been positively clustered against cells listed by Tree relationships. The reactivity pattern blocks are even more apparent, as is the lack of genetically meaningful association involving the six TAQ fragments.

Sequence analysis of DQA1 genes has identified eight distinct alleles (10). Six of the 8 occur commonly, and have been designated DQA1.1, DQA1.2, DQA1.3, DQA2, DQA3 and DQA4. RFLP patterns associated with reference panel cells that have been DQA1 allele typed are shown in Fig. 23. The first 8 cells listed (9005 to 9061) have the DQA1.1 sequence type. The ninth cell, 9056, is heterozygous for DQA1.1 and DQA1.2. These nine cells have two fragments in common (KPN 1042; TAQ 256). The next 8 cells (to 9008) are DQA1.2. The sequence type of cells 9008 and 9082 is not known. The next 5 cells (9011 to 9060) are DQA1.3. DQA2 cells are associated with DR7. MSP 605 is unique for DQA2. DQA3 is associated with DR4 and DR9 cells, and identified by MSP 215. DQA4 is present in cells expressing DR3, 5, and 8. Two fragments (HID 579; EC1 1107) characterize DQA4.

4.3 DPA

Forty-nine fragments were detected using the DPA locus probe. Positive cluster analysis of these 49 fragments is shown in Fig. 24 in which the cells have been listed primarily by DPw type assigned on the basis of cellular typing. There are two major clusters at the DPA1 locus. Heterozygous cells are seen at the interface between the two clusters (Nos. 9106, 9021, 9070, 9088, 9056 and 9009). Equally apparent is the greater pattern fragment variation associated with the less frequent cluster (top left) relative to that of the more frequent cluster. The first cluster stratifies DPw types mainly into DPw1, DPw5 and DPw1/5-associated New alleles (11). The second cluster comprises DPw3, DPw2 and DPw4 types. Subgroups of this second cluster are delineated by fragment TAQ 1207 which correlates closely with DPw2-assigned cells, while fragment BAM 900 extends to include a subgroup of DPw4 cells that are independently known to have the DPB1 locus sequence type DPB4.2. (11). These DPw2 and DPw4 subgroup cells are seen to be associated with a 'reciprocal' absence of fragments TAQ 1321, ECV 750 and BAM 867. The absence of fragment BGL529 extends to include the remaining DPB4.2 cells.

The two BGL fragments 724 and 529 (Fig. 24, columns 8 and 9 from right side) comprise a mutually exclusive pattern. Since they do not correlate with the two main clusters of DPA1, they

are interpreted to reflect polymorphism associated with the DPA2 locus.

5. Class II Beta loci

It is necessary to describe the procedure which has been adopted in this summary report for selection of informative fragments for the three class II beta loci. In the 10IW, the underlying concept for data analysis of class II beta probe patterns was to identify locus-specific fragments and the primary locus association of each cross-hybridizing fragment. This concept was incorporated into the data reporting in that relative hybridization strengths were converted into a locus assignment pattern. These patterns are shown in each of the probe/enzyme system reports (this volume). Each class II beta probe summary report utilized the primary locus assignment in order to identify the locus-specific, serospecificity-associated, fragment patterns.

We have re-examined the entire fragment data generated by each probe in order to assess locus assignment of all 639 class II beta fragments independent of hybridization strengths and of the deduced locus assignment.

The three class II beta probe fragments were considered in turn. Two hundred thirty-eight (238) fragments were obtained with the DRB probe, 225 with the DQB probe, and 176 with the

DPB probe. For DRB, then DQB, and finally DPB, all fragments were subjected to negative clustering with cells listed by DR, by DQ, and by DP specificities for each probe. Fragments were selected if their patterns correlated with cells grouped according to probe-related specificities. For example, based on the negative cluster of the 238 DRB fragments (Figs. 25a and 25b), 176 fragments were selected. The negative cluster of the selected 176 fragments is shown in Figs. 26a and 26b. Confirmation of the validity of fragment selection is depicted in the Tree analysis (Fig. 27). The fragments selected for each probe were compared with those described in the probe summary reports. The selected fragments were also compared with the data presented in Tables 2 and 3 which represent a synthesis of presumed locus-specific 'unique' fragments from system reports, probe reports and central data analysis. There was good concordance between fragments selected by the workshop standardization centers based on locus assignment and that obtained by our final analysis.

5.1 DRB

Figs. 28a and 28b show the positive cluster of 176 DRB locus-selected fragments with cells listed according to Tree relationships revealed in Fig. 27. The blocks of fragment patterns display a very close correlation with the serologically and cellularly defined DR and Dw specificities. Table 2 lists the 'unique' fragments for DR specificity

identification. Each of the 134 fragments, together with co-clustering fragments, can be identified in Figs. 28a and 28b. From Table 2, it can also be seen that there are fragments which correlate strongly with the DRw52 supertypic specificity, and with the three cellularly defined DRw52 subtypes, Dw24, Dw25 and Dw26. DRw8 positive cells are also associated with the DRw52 supertypic specificity. It has been suggested that these cells may comprise an unique subtype within DRw52. However, there is no evidence from the negative cluster of DRB RFLP patterns (Fig. 26) of any unique RFLP cluster mutually exclusive with those fragments associating with Dw24, Dw25 and Dw26 specificities.

Concerning DRw53, there are some 30 fragments which react en bloc with the 19 DRw53 positive cells (Figs. 28a and 28b). A few fragments (e.g. BAM 780, ECI 1513) are not present in all DRw53 positive cells, raising the possibility of DRw53 polymorphism.

5.2 DQB

The 225 RFLP fragments detected by the DQB probe are shown as a negative cluster in Figs. 29a and 29b. Of the 225, 94 were selected as informative for the serologically detectable DQ specificities. Of the 101, 53 are 'unique' fragments for particular DQ specificities (Table 3). In Figs. 30a and 30b the co-clustering patterns among the 94 fragments can be seen.

Fig. 31 is a positive cluster with cells listed according to their Tree relationships, in which the fragment columns have been repositioned to illustrate the block patterns associated with DQ serospecificities.

## 5.3 DRB, DQA and DQB

In this section, all fragments detectable by DRB, DQA and DQB probes have been considered together. From these 536 fragments, 187 have been selected as 'unique' RFLP fragments for DRB and DQB locus specificity assignment (see Tables 2 and 3). Fig. 32 shows the Tree relationship of the 70 cells using the total 536 fragments. Figs. 33a-d shows all 536 fragments associated with the DRB, DQB and DQA loci against the cells listed by Tree relationships, showing DQ, Dw and DR types for each cell. Comparison with Tables 2 and 3 enables the 'unique' fragments to be identified. The well-defined, 'block' fragment patterns are shown in Figs 33a, 33b, and the left half of Fig. 33c. The last columns of Fig. 33d (HIC 228 to end) show fragments whose reactivity patterns are not well defined, but which may become so on further analysis. They are included for completion. Between the two groups of fragments are those associated with the DQB2 and DQA2 loci (PVU 722 to MSP 562). These patterns are considered in more detail in Section 6.2.

From the practical standpoint of DNA typing for DR and DQ specificities using RFLP, it is valuable to consider the cluster patterns created by combinations of the three most relevant probes (DRB, DQA and DQB). The data presented in this section enables selection of a limited number of probe/enzyme combinations sufficient for definition of DR, Dw and DQ haplotypes. The haplotype discriminatory power of any particular probe/enzyme combination can also be assessed. This enables a balance to be reached between minimizing probe/enzyme combinations, on the one hand, and achievement of adequate haplotype characterization, on the other. An example of such an approach can be found in Martell et al. (this volume - 12) in which DRB TAQ, DQB TAQ and DQB BAM were selected. Fig. 34 is a positive cluster involving 72 fragments arising from these two probes and two enzymes. Note that it has not been possible to delete the DRB BAM fragments in the computer-assisted analysis.

5.4 DPB

The DPB probe recognized 176 fragments. Only some 53 fragments were specific for the DPB1 and DPB2 loci. The majority of the remaining 123 correlated with DR specificities. The most likely explanation for the DPB probe associations with DR specificities is cross-hybridization due to homology between the cDNA probe and DR region sequences. The possibility exists that any such sequence homology has

arisen from donation of DR gene sequences to the DP locus by some gene rearrangement process. It is noteworthy that there is no comparable association with DQw specificities, except for DQw5. These patterns provide information for more detailed examination of evolutionary relationships between and within the three class II beta loci.

In Fig. 35, 154 selected DPB probe-detectable fragments are shown against cells listed according to DR type. Fig. 36 maintains the same order of the 154 fragments, but rearranges the cells according to DPw type. For the 54 DPw-specificity associated fragments, several groupings can be readily identified. The first two groups are those of the major clusters of the DPB1 locus. These are followed by fragments, the presence of which are informative in distinguishing between cells of different DPw and DPB sequence type. Then follows fragments characterizing the two major clusters of the DPB2 locus.

The first 12 fragments are clearly associated with the DPw1/w5/w3/New DPB1 cluster. Three fragments specify DPw1 (HIC 341, MSP 498, MSP 671). Fragment MSP 716 is present with DPw5 and with 4 of the 6 cells (9034, 9003, 9043 and 9048) designated 'New' in that no DPw specificity has been assigned. Fragment SST 1365 is present with the same four 'New' cells plus a fifth (No. 9047), and has additional reactivity. The

remaining DPB 'New' cell (9060) has a 'unique' pattern of fragment presence, and of fragment absence. From inspection, it can be seen that fragments PST 202, HID 186, TAQ 272 and ECI 1293 were absent only in this cell. Fragment SST 1742 is present only in cells 9047 and 9052. Both cells are DR7 and, by Tree analysis of cell relationships (Figs. 37 and 38), are seen to have a close evolutionary association, so it is not possible to determine whether the fragment is subtyping DR7 or truly reflects a new DPw specificity.

Attention is drawn to two fragments (BGL 728 and KPN 2444) which are primarily reactive with DPw2 and the DPB1 sequence of DPw4, DPB4.2 (11) along with some reactivity with cells in the DPw1/w5/w3 cluster. Fragments MSP 217 and MSP 438 appear to be specific for DPw2. Fragment SST 318 associates with the DPB1 allele, DPB2.2 (11). Another pair of fragments (BGL 505 and MSP 107) have reactivity patterns associated with DPw4. MSP 107 extends to include all 27 DPw4-associated homozygote cells, while BGL 505 is absent in all but 2 of the 9 DPB4.2 cells.

Fig. 37 depicts a Tree dendogram based on the use of all cells, heterozygous as well as homozygous at the DPB loci. In Fig. 38, DPB heterozygous cells have been removed, and the analysis repeated only on the 53 remaining homozygous cells. There is excellent stratification of cells into the two main

clusters of DPw1/w5/w3-associated cells and of DPw2/w4 related cells. The three 'blank' zones in which DPw specificities have not been assigned are clearly demarcated. The DPw4 related 'blank' comprises cells of the DPB1 allele, DPB4.2. (11). Cells 9104 and 9048 are seen to be DPw2-associated.

The RFLP pattern relationships between these cells, again listed according to DPw type, is shown in Fig. 39 which utilizes 45 fragments detectable by the DPA locus probe, as well as 53 detectable by the DPB probe. These relationships are considered in more detail elsewhere (11).

## 6. Class II Alpha and Beta loci fragment patterns, including linkage disequilibria.

### 6.1 Class II DRA,DQA1,DQA2,DPA1 and DPA2 loci

One hundred thirty-six RFLP fragments were associated with these five class II alpha loci. Figs. 40a and 40b show the fragment cluster pattern. It can be seen that fragments show intra-locus co-clustering. In no instance are the clusters composed of fragments detectable by more than one locus probe. Fig. 41 shows the Tree analysis of cell relationships generated by these class II alpha loci RFLP fragments. Although the alpha chain products are not the primary determinant of serologically-detectable specificities, it is

apparent that the cells are stratified into recognizable groups showing known DR and DQ type relations.

## 6.2 Class II DQA2 and DQB2 loci

During analysis of the 536 fragments detectable by the DRB, DQA and DQB probes, the similarity of mutually exclusive RFLP clusters for the two non-expressed DQ loci were apparent. (See Figs. 33c-d) In Figs. 42 and 43 this association is presented in more detail. Fig. 42 shows the negative cluster pattern with cells listed by Tree relationships. Fig. 43 is the corresponding positive cluster in which it can be seen that the less frequent DQA2 cluster is associated with two DQB2 clusters. The more frequent cluster has a very similar pattern for both DQA2 and DQB2. There is very clear stratification of DQw type in relation to these clusters. For example, all DRw8 DQw4 cells, together with the two unusual DQw7 cells (9016 and 9064), are associated with a particular pattern. Again, the DQw8 cells are predominantly associated with one of the two DQB2 subgroups comprising the less frequent cluster. These and other patterns clearly reveal associations of evolutionary significance.

## 6.3 Class II Inter-Locus Co-Clustering Fragments

Of the total 781 fragments detectable by class II alpha and beta probes, 175 fragments participated in clusters involving probes from two or more class II region loci. Figs. 44a-b

show the positive cluster pattern of these fragments against cells listed by DR type. This figure is of particular use in distinguishing between likely cross-locus hybridization, on the one hand, and genuine linkage disequilibrium, on the other.

## IV. ACKNOWLEDGEMENTS

The authors wish to acknowledge the invaluable contribution of Mr. Mark Ferguson of the Computing Center, Howard Hughes Medical Institute, University of Utah Medical Center, Salt Lake City, Utah. MJS wants to record his appreciation for the enthusiastic, secretarial support from Mrs. Percy Noble, which almost foundered on the 'unique' fragment tables.

TABLE 1

'Unique' RFLP fragments for Class 1 locus specificity assignment.

| RFLP Specificity A- | BAM | BGL | ECI | ECV | HID | KPN | MSP | PST | PVU | SST | TAQ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A1 | | | | | (476) | | | | | | |
| A2 | | | [1179] | [1355] | | | | | | | |
| A3 | | | 287 | | | | | | (1482) | | 62 |
| | | | 1083 | | | | | | | | 96 |
| A23,A24 | | (602) | | | (498) | (562) | | | | (592) | |
| A23,<A24 | | | | | | 1270 | | | | | |
| <A24 | | | | 664 | | | | | | | |
| A25,A26 | | | | | | 512 | | 430 | | | |
| A11 | 825 | 1123 | 1299 | | | 1570 | | | | | |
| A30 | | | 1381 | | | | 262 | | 1181 | 797 | |
| A31 | 536 | | | | (707) | | | 143 | 549 | | |
| <A31 | | | | | | | | | (1619) | | |

| RFLP Specificity B- | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| B8 | 2356 | | | (786) | | | | | | | |
| Bw41 | | | | | 1491 | | | | | | |
| Bw41,Bw42 | 250 | | | | | | | (79) | | | |
| <B44 | 778 | 948 | | | | | | | | 528 | |
| Bw47 | | | | | | | | 172 | | | |
| <B51 | | | | | | | | | | 278 | |
| <Bw57 | | (747) | | | | | | | | | |
| Bw60 | | | | | 993 | | | | | | |
| Bw61,<Bw60 | | | | | 2644 | | | | | | |

| RFLP Specificity C- | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cw4 | | | | 1096 | | | | | | | |
| Cw7 | | | | | | | | 101 | | | |
| <Cw7 | 1343 | | | | | | | | | | |
| C blank | | | | | | | 427 | | | | |

## FOOTNOTES TO TABLE 1

1. Unique RFLP fragments have been defined as those fragments which correlate completely with the latest HLA type assigned to each workshop cell. Since the workshop cells include those having variant/atypical fragment reactivity patterns, the definition has been extended to include fragments with either a single reactivity in excess of the stated specificity, or a single reactivity less than the stated specificity. Such fragments are identified in using () for additional reactivity and [] for deficient reactivity. The cells corresponding to both types of parentheses are listed below in this footnote (4).

2. Other fragments exist which have reactivity, or lack of reactivity, with two or more cells apart from that with the primary specificity. Some of these fragments, particularly those with reactivity to only a limited number of cell specificities, and those with higher frequency reactivity but in which the reactivity correlates closely with several specificities, are also useful for HLA specificity typing.

3. The figure showing fragment patterns using probes for the class I loci includes all 204 fragments. Specificity-unique fragments are identifiable by a * at the top of each column. Since the figure has been produced by reordering the fragment columns generated by both positive and negative cluster analysis, fragments having reactivity patterns related to the starred, unique 'key' fragments can be readily identified.

TABLE 1 - FOOTNOTE 4

| RFLP Specificity A- | Fragment | Cell Number |
|---|---|---|
| A1 | HID 476 | (6) |
| A2 | ECI 1179 | [32] |
| A2 | ECV 1355 | [7,69] |
| A3q | PVU 1482 | (6) |
| Aw23,Aw24 | BGL 602 | (18) |
| Aw23,Aw24 | HID 498 | (18) |
| Aw23,Aw24 | SST 592 | (18) |
| Aw23,Aw24 | KPN 562 | (48) |
| Aw31 | HID 707 | (42) |

| RFLP Specificity B- | | |
|---|---|---|
| B8 | ECV 786 | (70) |
| Bw41,Bw42 | PST 79 | (63) |
| <Bw57 | BGL 747 | (66) |

TABLE 2

'Unique' RFLP fragments for DRB locus specificity assignment.

| RFLP Specificity D- | BAM | BGL | ECI | ECV | HIC | HID | KPN | MSP | PST | PVU | SST | TAQ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DR1, Dw1 | | (RB696) | RB1006 | RB183 | | RB302 | QB1775 | (RB493) | | RB657 | RB1159 | (RB580) |
| DR1, Dw20 | | | | RB630 | | RB343 | | | | | | |
| | | | | | | RB610 | | | | | | |
| DR1, Dw1 | | | | | | | | | RB142 | | | |
| DR1, Dw20 | | | | | | | | | RB373 | | | |
| DR2 | | | RB628 | | | RB332 | | | | RB447 | (RB1319) | |
| <DR2 | | RB1455 | | | | | | | | | | |
| DR15, Dw2 | | | | | | | | RB381 | | | (RB615) | (RB142) |
| DR15, Dw12 | | | | | | | | | | | | (RB212) |
| DRw15, Dw2 | | | | | | | | | | | | (RB123) |
| DRw15, Dw12 | | | | | | | | | | | | |
| DRw16, Dw21 | | | | | | | | | | | | |
| DRw16, Dw21 | | | | | | | | | | | RB1030 | RB169 |
| DRw16, Dw22 | | | | | | | | | | | | |
| DRw16, Dw22 | | (QA382) | | | | | | | | | | |
| DRw17, Dw3 | | | | (QB1514) | | QB1142 | QA2520 | | | | | |
| DRw17, Dw3/24 | | | | | | | | | | | RB2396 | |
| DRw17, Dw3/25 | | | | | | RB255 | | | | | | |
| <DRw11, Dw5 | | | | | | | | | (RB538) | | | |
| DRw11, DB2 | | | | | | | | | | | | |
| DRw12 | | | | | | RB183 | | | | RB592 | | |
| DRw13, Dw18 | | | | | | (QA768) | | | | | RB1287 | |
| | | | | | | | | | | | QA1553 | |
| DRw13, Dw19 | (QA2393) | | | RB1096 | | RB270 | [QB1175] | | RB632 | RB1483 | (RB1375) | |
| | | | | | | | | | QB643 | | | |
| DRw14, Dw16 | | | | | | | (QA1836) | | | | | |
| | | | | | | | (QB1544) | | | | | |
| DRw8 | | | | | | | | | | | | RB866 |

TABLE 2
(Continued)

| RFLP Specificity D- | BAM | BGL | ECI | ECV | HIC | HID | KPN | MSP | PST | PVU | SST | TAQ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DR7 | | | | | | | | QA605 | (RB215) | RB475 | | |
| DR7, DB1 | | | (RB1533) | (RB2047) | | (QB1280) | RB943 | | RB490 | (QB478) | QB540 | |
| DR7, Dw17 | | | | (QB2001) | | | (QB920) | | | | | RB260 |
| <DR7, DB1 | | | | | | | | | | | | RB723 |
| DR7, Dw17 | | | | | | | | | | | | |
| DR7, DW11 | | | | (QB1643) | | (RB966) | | | | | QA2355 | |
| <DR7, DB1 | | | | | | | | | | | | |
| DR7, Dw11 | | | | | | | | | | | | |
| DRw9, Dw23 | | | | | | RB172 | | | (QA912) | | | |
| DR4 | RB526 | RB1027 | | RB2298 (QB1452) | [RB1077] | (RB158) | | RB368 (QA215) | RB205 RB355 RB411 | RB565 | | RB522 |
| DR4, DQw7 | | | | | (RB411) | | | | | | | |
| DR4, DQw8 | | | | | | | | | [QB396] QB684 | | | |
| DRw52 | | | | RB1824 | | RB296 | | | | | | |
| DRw52*[DRw8] | [RB1133] | RB916 | RB946 | RB752 [RB1534] | | | | | | | [RB1125] | |
| DRw52, Dw24 | | | | | | | RB272 RB769 | | RB107 | | | |
| DRw52, Dw25 | | | | [RB2004] | | | | | | | | [RB1148 |
| DRw52, Dw26 | QA2393 | | | RB1096 | | RB270 | [QB1175] | | RB632 [QB643] | RB1483 | (RB1375) | |
| DRw53 | RB428 RB463 RB659 QA763 | RB564 | RB373 RB398 RB410 RB1255 (RB1198) QA634 | RB1648 | | RB144 RB313 RB717 QA483 | QA1176 | RB115 RB176 | QA232 | RB388 RB517 RB616 RB1350 [RB460] | RB519 RB1095 RB2112 | RB284 |

* Signifies DR3, 5, 6, excluding DRw8.

## FOOTNOTES TO TABLE 2

1. Unique RFLP fragments have been defined as those fragments which correlate completely with the latest HLA type assigned to each workshop cell. Since the workshop cells include those having variant/atypical fragment reactivity patterns, the definition has been extended to include fragments with either a single reactivity in excess of the stated specificity, or a single reactivity less than the stated specificity. Such fragments are identified in using () for additional reactivity and [] for deficient reactivity. The cells corresponding to both types of parentheses are listed below in this footnote (6).

2. Fragments typed in bold were identified in the DRB and DQB loci 'antigen' reports. Fragments in plain type have been added during this review procedure. Fragments detected with the DQ beta probe that reflect cross-hybridization with DR beta specificity associated sequences have not been included.

3. Other fragments exist which have reactivity, or lack of reactivity, with two or more cells apart from that with the primary specificity. Some of these fragments, particularly those with reactivity to only a limited number of cell specificities, and those with higher frequency reactivity but in which the reactivity correlates closely with several specificities, are also useful for HLA specificity typing.

4. The figure showing fragment patterns using probes for the DRB, DQA and DQB loci includes all 536 fragments. Specificity-unique fragments are identifiable by a * at the top of each column. Since the figure has been produced by reordering the fragment columns generated by positive cluster analysis, fragments having reactivity patterns related to the starred, unique 'key' fragments can be readily identified.

5. From the workshop data, it is not possible to be certain of the primary locus of reactivity for three groups of fragments. They are:

| | | | |
|---|---|---|---|
| (1) | DRw13, Dw19 | - | DRw52, Dw26 |
| (2) | DR1, Dw1/20 | - | DQw5, DR1 |
| (3) | DRw17, Dw3 | - | DQw2.3 |

The fragments for these three groups are listed in the corresponding two locations.

TABLE 2 - FOOTNOTE 6

| RFLP Specificity D- | Fragment | | Cell Number |
|---|---|---|---|
| DR1 | TAQ | RB580 | (32) |
| | BGL | RB696 | (25) |
| | MSP | RB493 | (16) |
| DR2 | SST | RB1319 | (37) |
| DR15 | SST | RB615 | (37) |
| | TAQ | RB142 | (37) |
| | TAQ | RB212 | (37) |
| DRw15 | TAQ | RB123 | (37) |
| DRw16 | BGL | QA382 | (43) |
| DR17 | ECI | QB1514 | (64) |
| <DRw11 | PST | RB538 | (60) |
| DRw13 | HID | QA768 | (105) |
| | SST | RB1375 | (92) |
| | KPN | QB1175 | [56] |
| | PST | QB643 | [56] |
| DRw14 | KPN | QA1836 | (52) |
| DRw8 | PST | QA912 | (75) |
| DR7 | PST | RB215 | (75) |
| | ECI | RB1533 | (75) |
| | ECV | RB2047 | (75) |
| | PVU | QB478 | (52) |
| | HID | QB1280 | (106) |
| | KPN | QB920 | (106) |
| | ECV | QB1643 | (106) |
| | HID | RB966 | (106) |
| DRw9 | PST | QA912 | (66) |
| DR4 | HIC | RB1077 | [7] |
| | HID | RB158 | (7) |
| | ECV | QB1452 | (75) |
| | MSP | QA215 | (75) |
| | HIC | RB411 | (31) |
| | PST | QB396 | [106] |

TABLE 2 - FOOTNOTE 6
(Continued)

| RFLP Specificity D- | Fragment | | Cell Number |
|---|---|---|---|
| DRw52 | BAM | RB1133 | [37],(28) |
| | SST | RB1125 | [37] |
| | ECV | RB1534 | [60] |
| | ECV | RB2004 | [60] |
| | TAQ | RB1148 | (37) |
| | KBN | QB1175 | (56) |
| | SST | RB1375 | (92) |
| DRw53 | ECI | RB1198 | (20) |
| | PVU | RB460 | [106] |
| DQw1 | KPN | QB515 | (45) |
| | ECI | QB383 | (37) |
| | HIC | QB850 | (37) |
| | SST | QB228 | (37) |
| DQw6.1 | BAM | QB289 | (37) |
| | TAQ | QB287 | (37) |
| | TAQ | QB261 | (37) |
| DQw2 | PVU | QB63 | (106) |
| | ECV | QB158 | (106) |
| | PVU | QB166 | (11,66) |
| | TAQ | QB87 | (11,66) |
| DQw2.3 | ECV | QB1514 | (64) |
| DQw2.7 | ECV | QB2001 | [106],(75) |
| | HIC | QB766 | [106] |
| | PVU | QB540 | (106) |
| | PVU | QB478 | (52) |
| | TAQ | QB669 | (11,66) |
| DQw7 | KPN | QB120 | (45) |
| | KPN | QB533 | (45) |
| | PVU | QB34 | (45) |
| | SST | QB222 | (37) |
| | SST | QB286 | (37) |
| | TAQ | QB100 | (37) |
| | BAM | QB355 | (37) |
| DQw8 | PST | QB396 | (7) |

TABLE 3

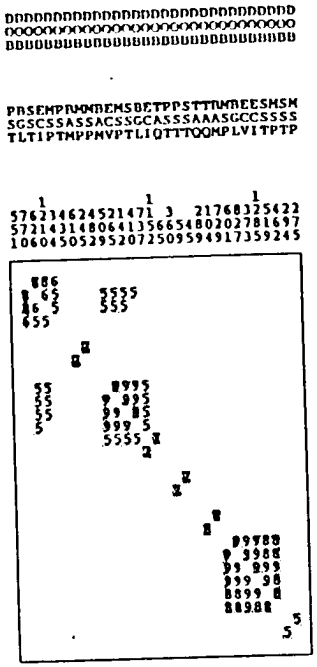
'Unique' RFLP fragments for DQB locus specificity assignment.

| RFLP Specificity D- | BAM | BGL | ECI | ECV | HIC | HID | KPN | MSP | PST | PVU | SST | TAQ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DQw1 | | | (QB383) | | | QB644 | (QB515) | | | | (QB228) | QB534 |
| <DQw1 # | | | | QB673 | (QB850) | | | | | | | [QA245] |
| DQw5 | QB576 | | | QB262 | | | [QA1042] | | QB136 | | | |
| | | | | QB271 | | | | | | | | |
| DQw6 | | (QB310) | | | | | | | | | | |
| <6.Dw2/18/19* | | | QB226 | QB524 | | | | | | | | |
| | | | QB922 | | | | | | | | | |
| <6.Dw2/18* | (QB289) | | | | | | | | QB1068 | QB217 | | (QB287) |
| | | | | | | | | | | | | (QB261) |
| <6.Dw12/8.3* | QB872 | | | QB1182 | QB185 | | | | | QB202 | | QB450 |
| | | | | | QB1536 | | | | | | | |
| DQw2 | QB383 | | | | | | | | | [QB63] | | [QB158 |
| | | | | | | | | | | (QB166) | | (QB87) |
| DQw2.DR3 + | | | | (QB1514) | | QB1142 | | | | | | |
| DQw2.DR7 + | | | | (QB2001) | [QB766] | QB1280 | QB920 | | | [QB478] | [QB540] | (QB669) |
| DQw7 | [QB355] | | | | | QB341 | [QB120] | | | QB372 | [QB222] | [QB100] |
| | | | | | | | [QB533] | | | [QB34] | [QB286] | |
| DQw8 | | | | | | | | | [QB396] | | | |
| | | | | | | | | | QB684 | | | |

# Four fragments identify a subgroup of DQw1. The four are present in all DQw5 and DQw6 cells except for cells 9011 and 9066. These two DQw6 cells are identified as the DQw6.Dw12/8.3 subgroup (see below).

* There are unique RFLP fragments for three DQw6 subgroups. Since the three subgroups are associated with particular Dw types, they have been identified as: DQw6.Dw2/18/19; DQw6.Dw2/18; and DQw6.Dw12/8.3.

\+ There are unique RFLP fragments for two DQw2 subtypes corresponding to the DR3 and the DR7 haplotypes.

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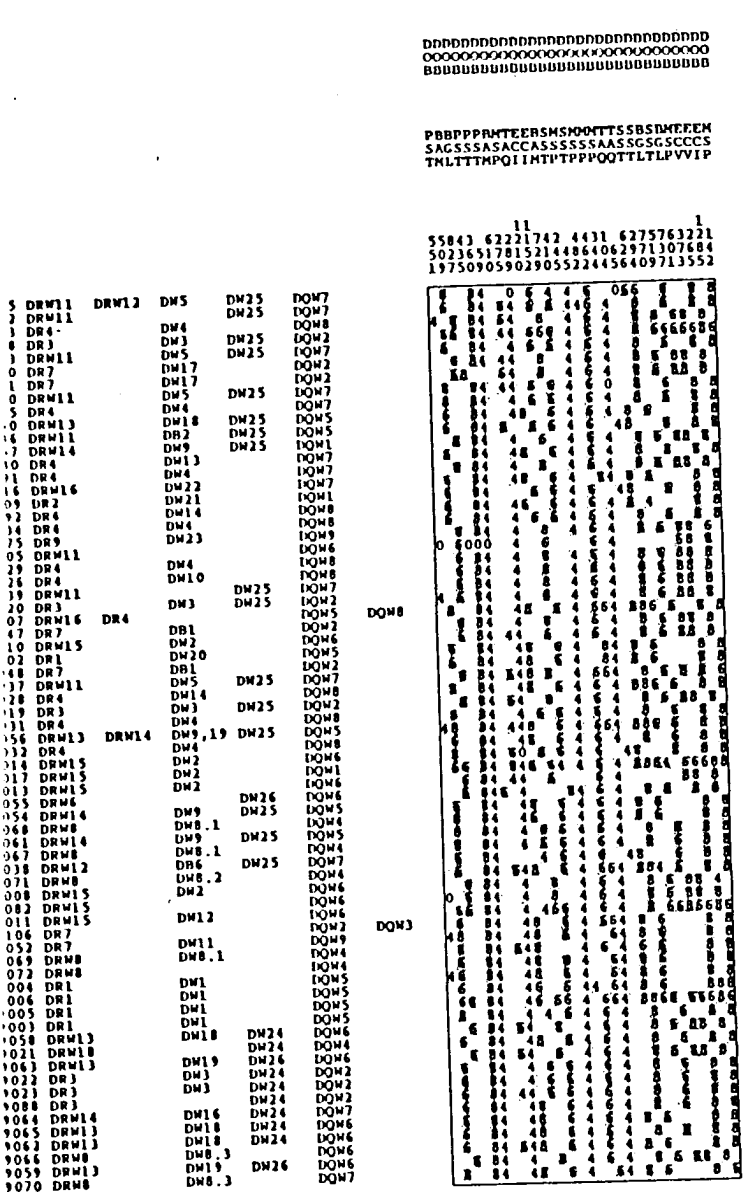
Class II DOB locus RFLP fragments (30). Fragment cluster.

Page 1 of 1

Fig. 1

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Class II DOB locus RFLP fragments (30). Negative Cluster.

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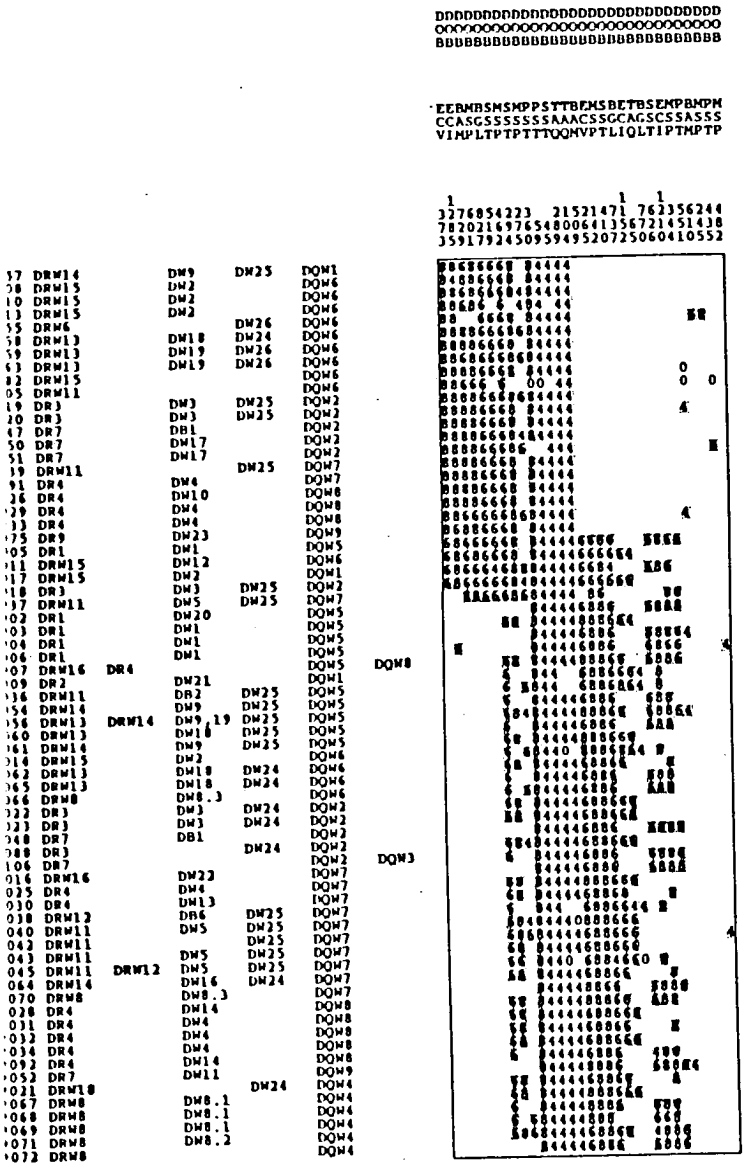
Fig. 2



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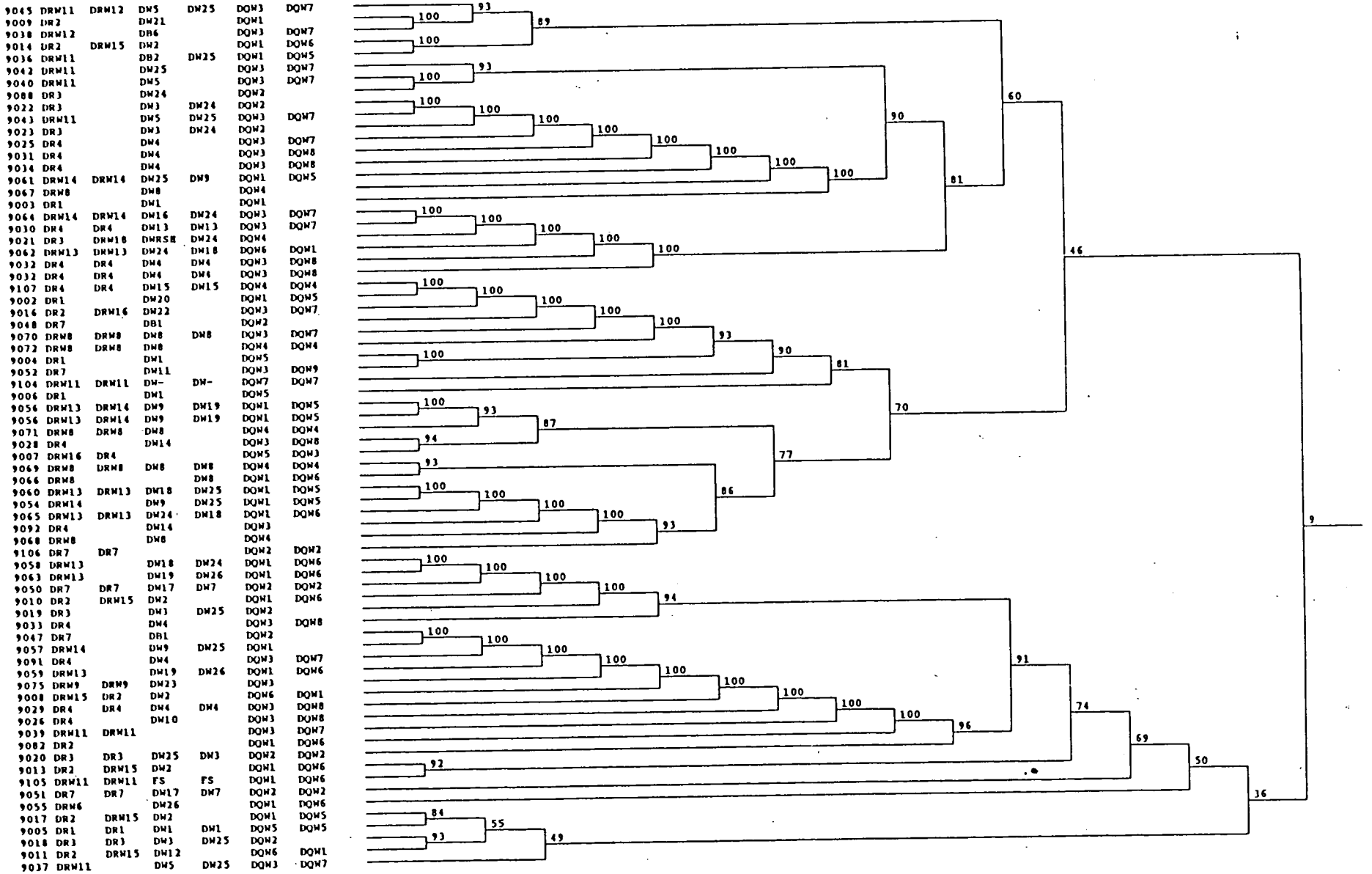
Class II DOB locus RFLP fragments (30). Cells listed by DQ specificity groups.



Fig. 3

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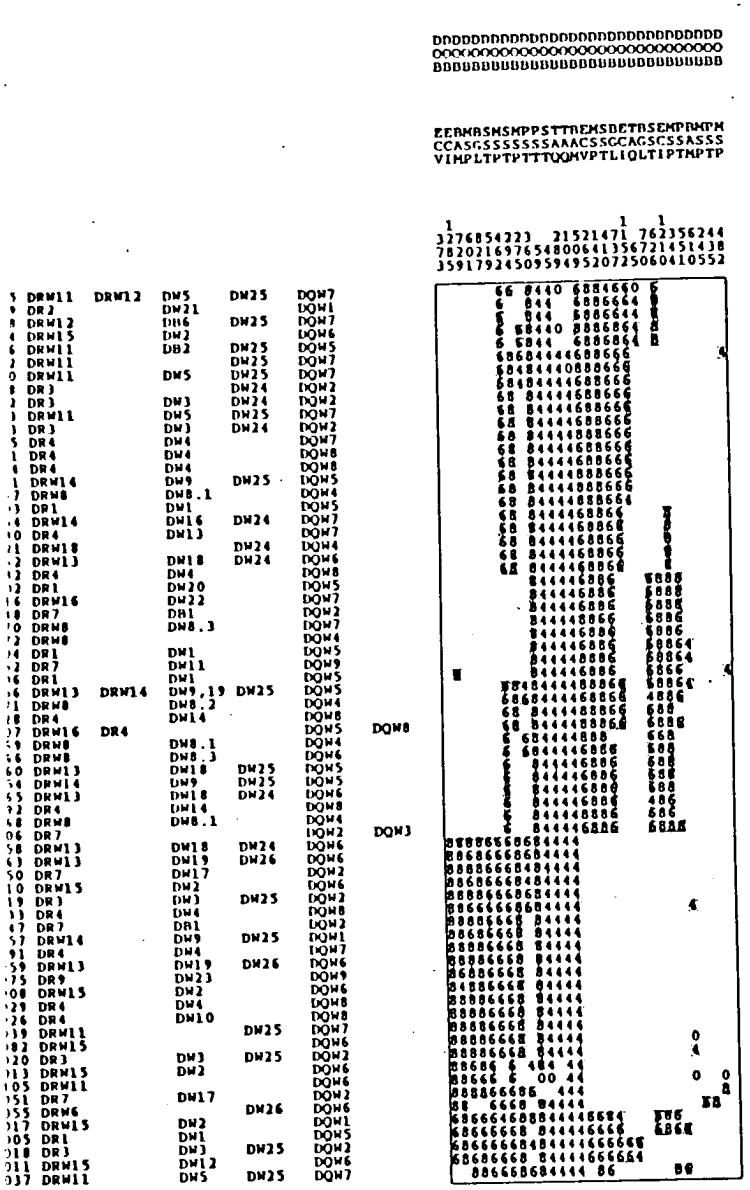
Tree analysis of cell relationships: DOB locus.

Fig. 4



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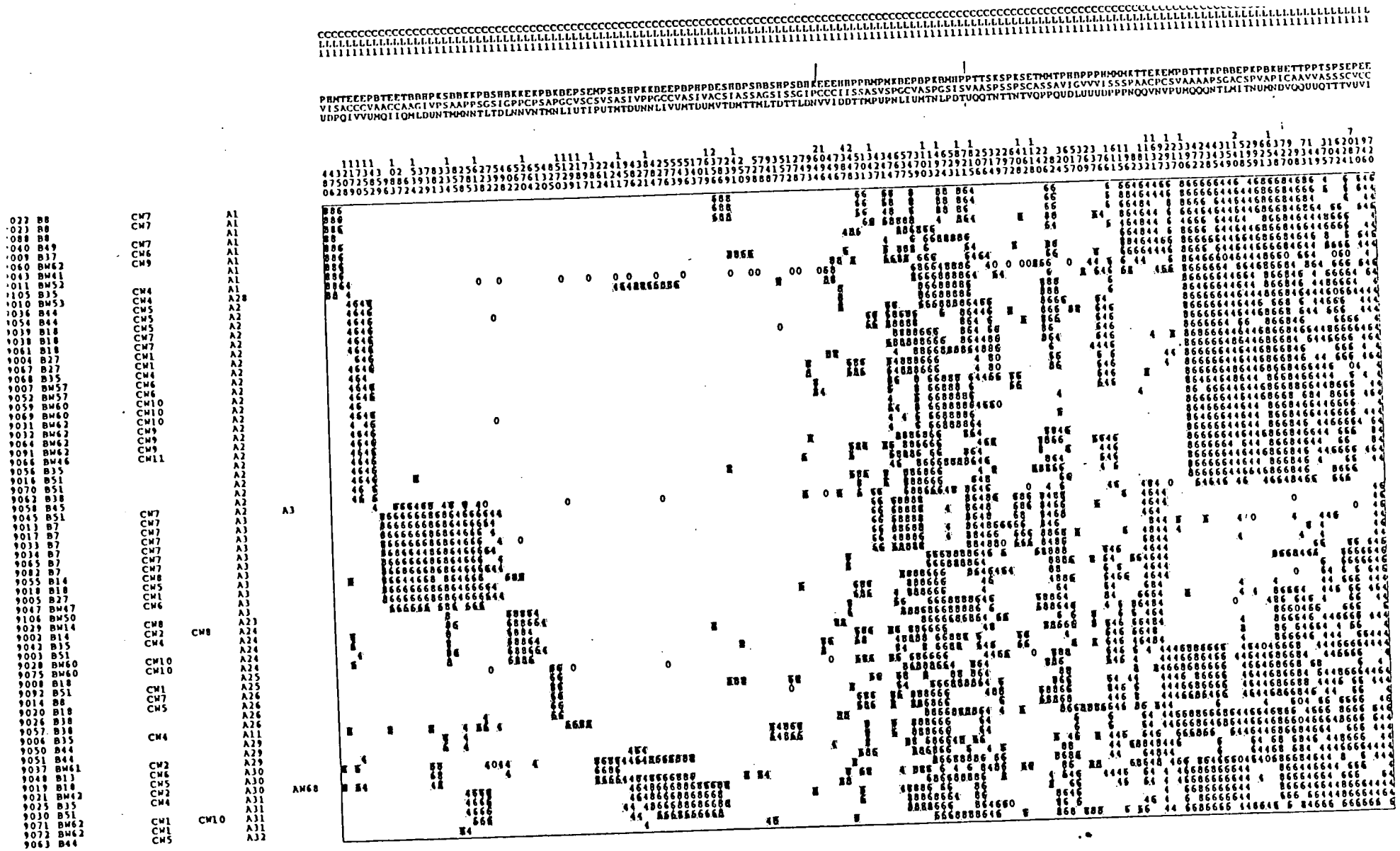
Class II DOB locus RFLP fragments (30). Cells listed by Tree relationships.



Fig. 5



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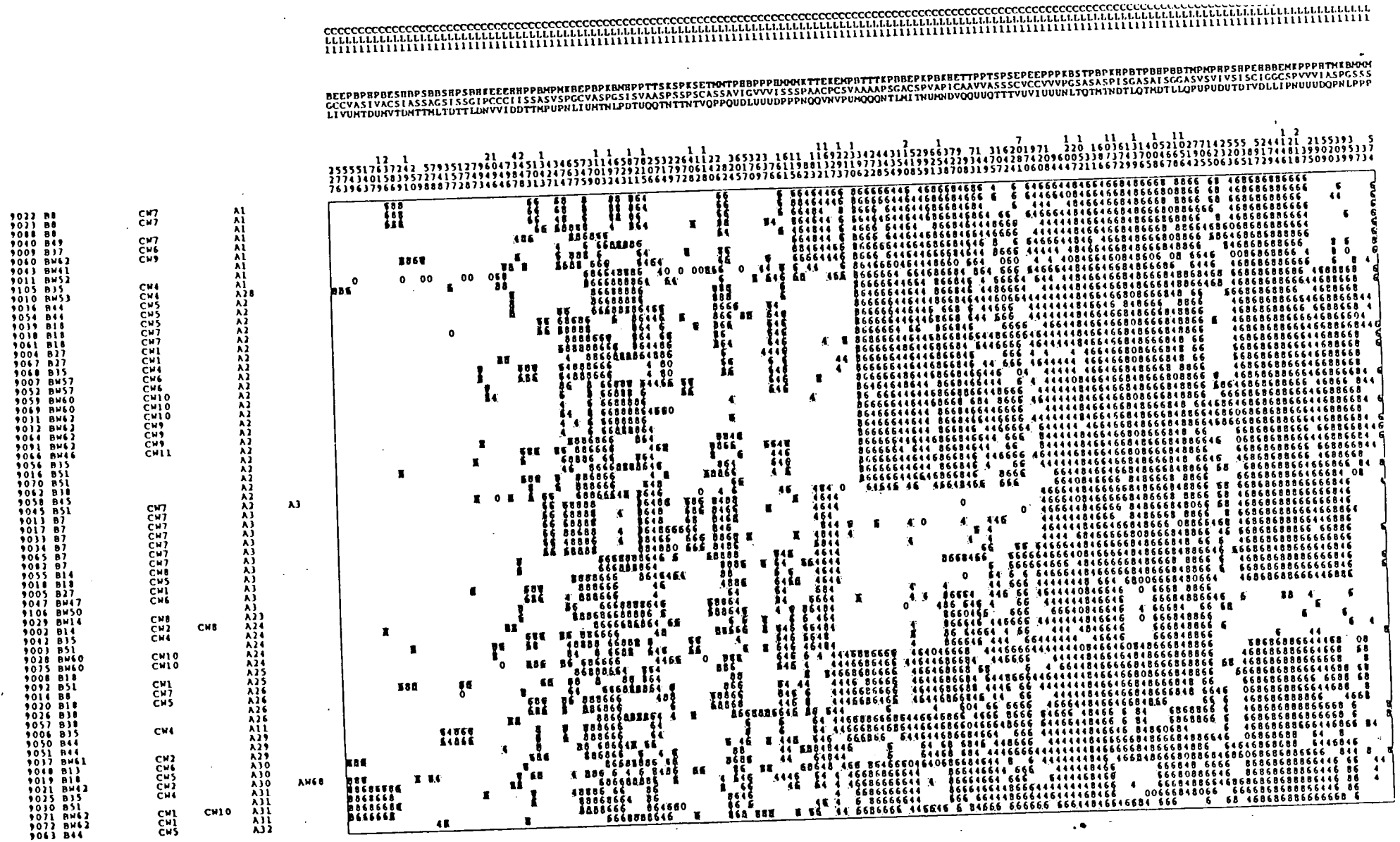
Class I loci RFLP fragments (204). Positive cluster. Cells listed by A locus type.



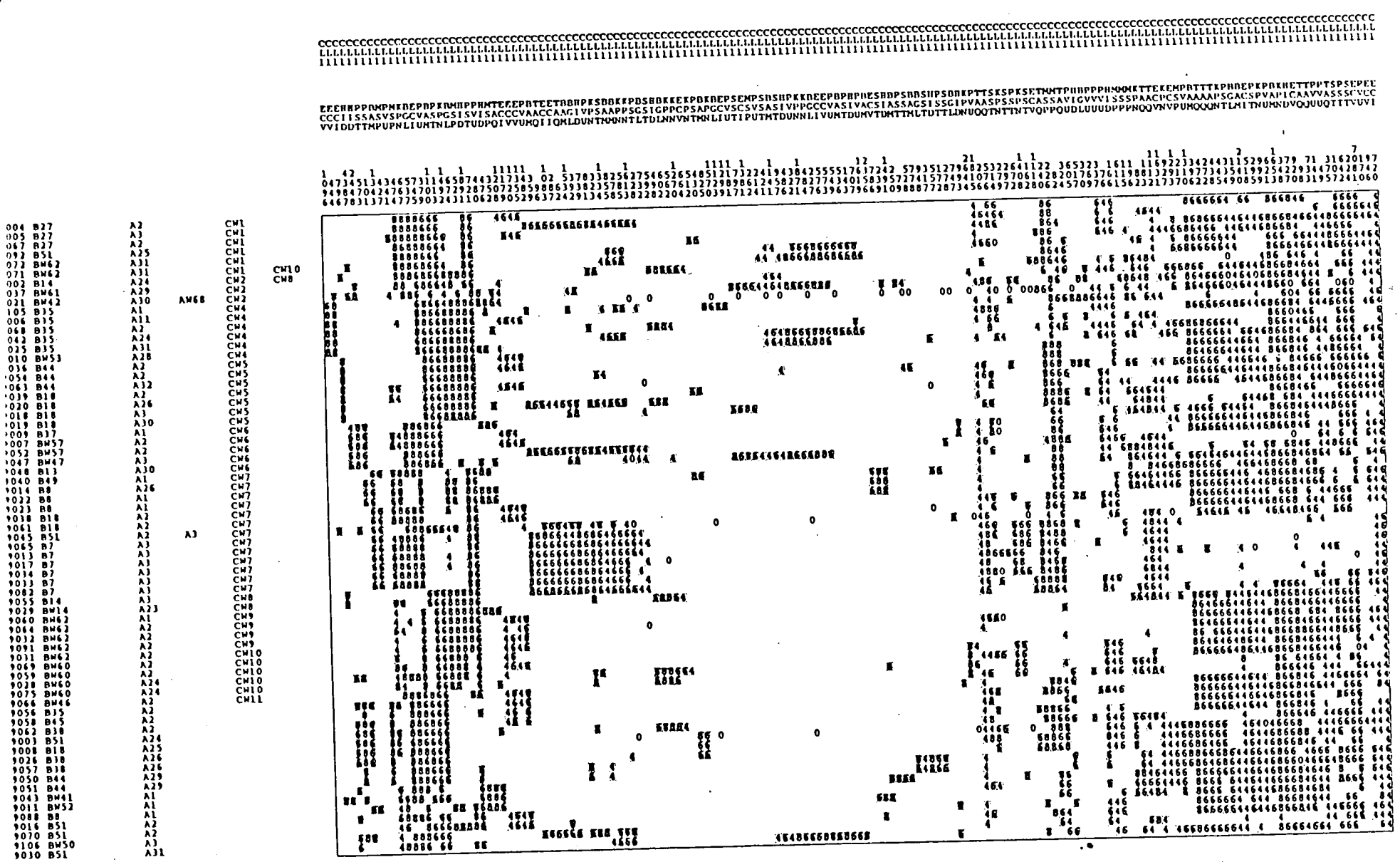
Fig. 6a



Tenth International Histocompatibility Workshop
Class I loci RFLP fragments (204). Positive cluster. Cells listed by A locus type.



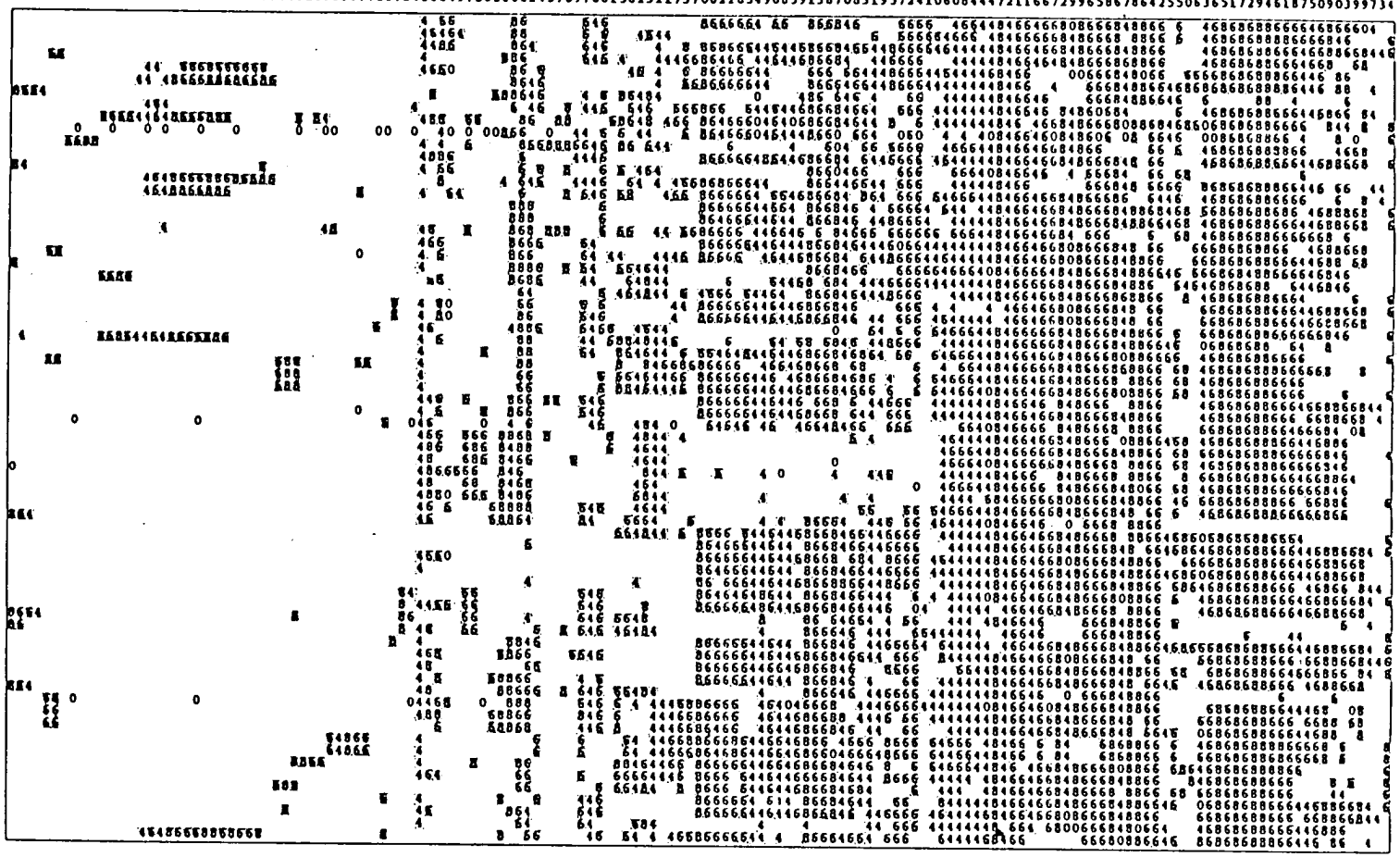
Fig. 6b



Tenth International Histocompatibility Workshop
Class I loci RFLP fragments (204). Positive cluster. Cells listed by C locus type.



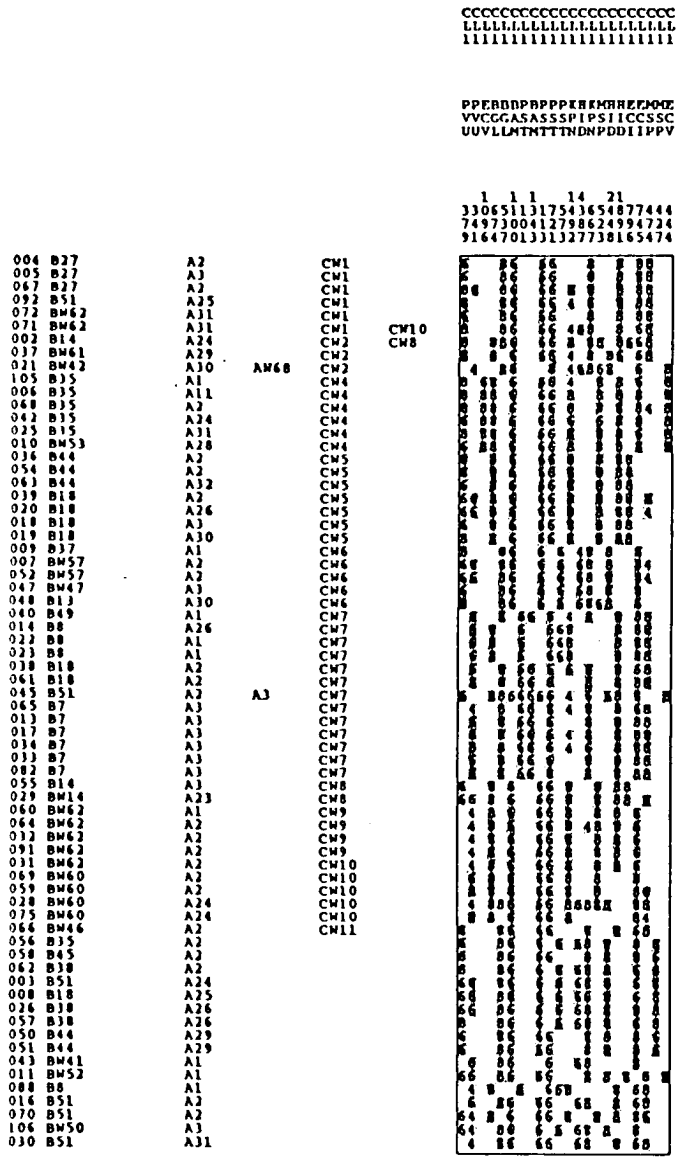
Fig. 7a



Tenth International Histocompatibility Workshop
Class I loci RFLP fragments (204). Positive cluster. Cells listed by C locus type.



Fig. 7b



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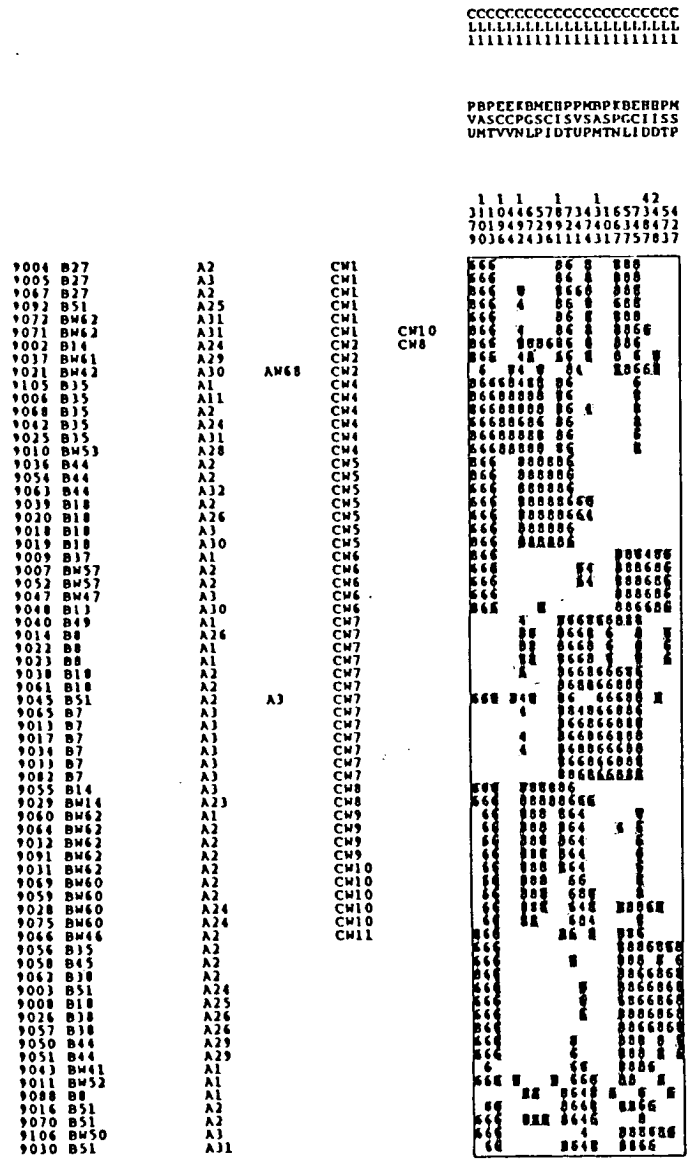
Class I C locus-associated RFLP fragments (22). Negative cluster.



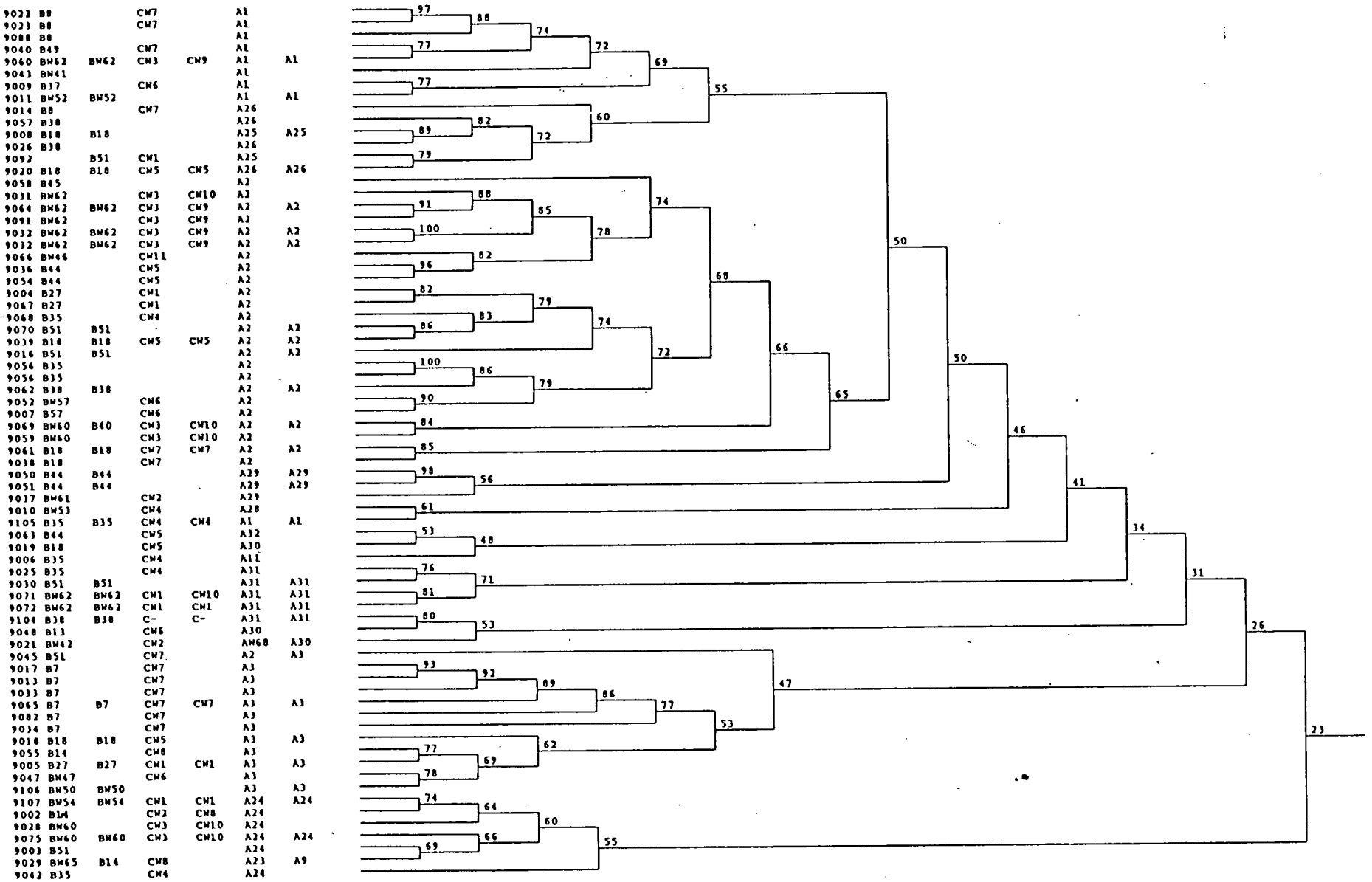
Fig. 8



Tenth International Histocompatibility Workshop
Class I C locus-associated RFLP fragments (22). Positive cluster.

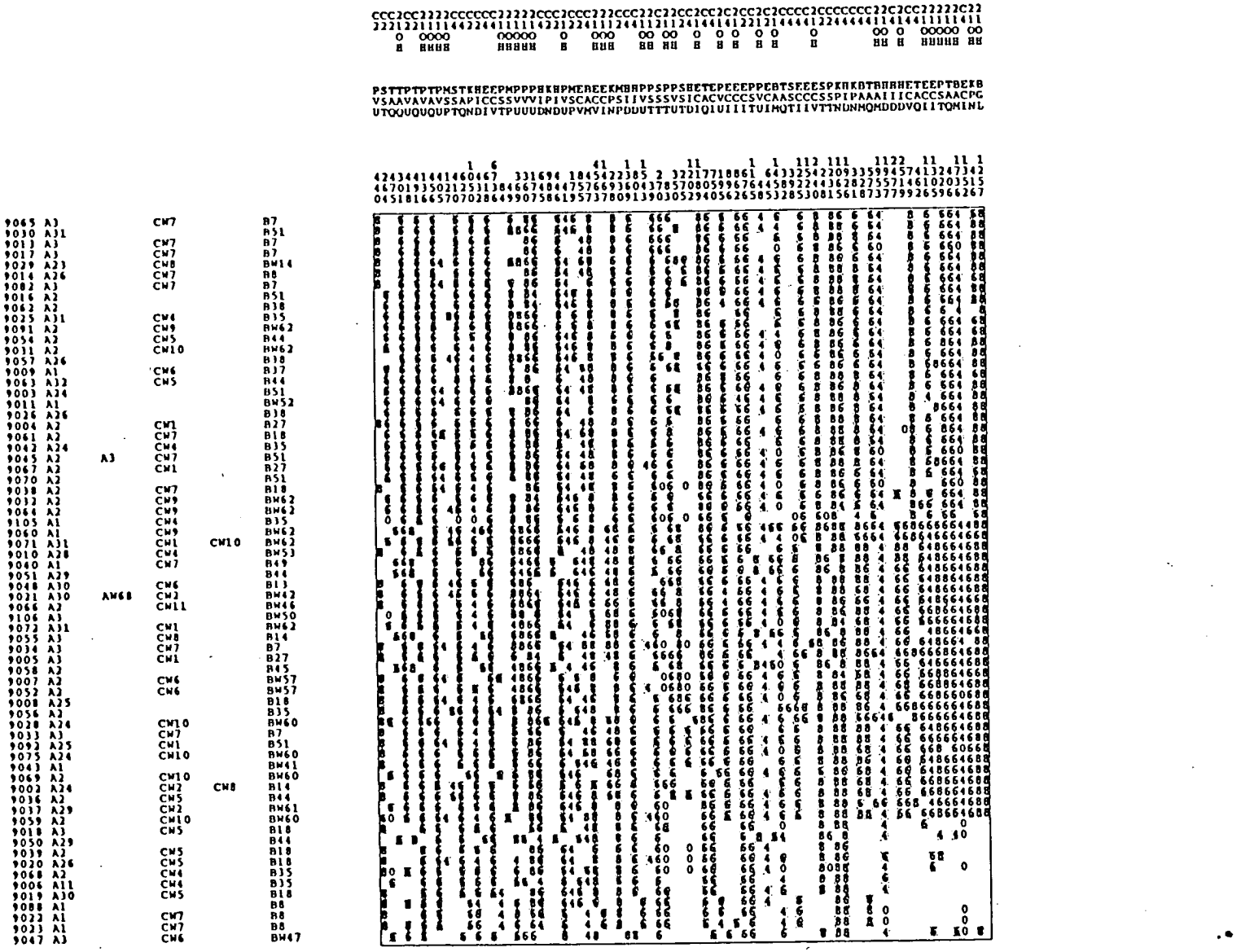


Fig. 9




Tenth International Histocompatibility Workshop
Tree analysis of cell relationships: Class I RFLP fragments (207).

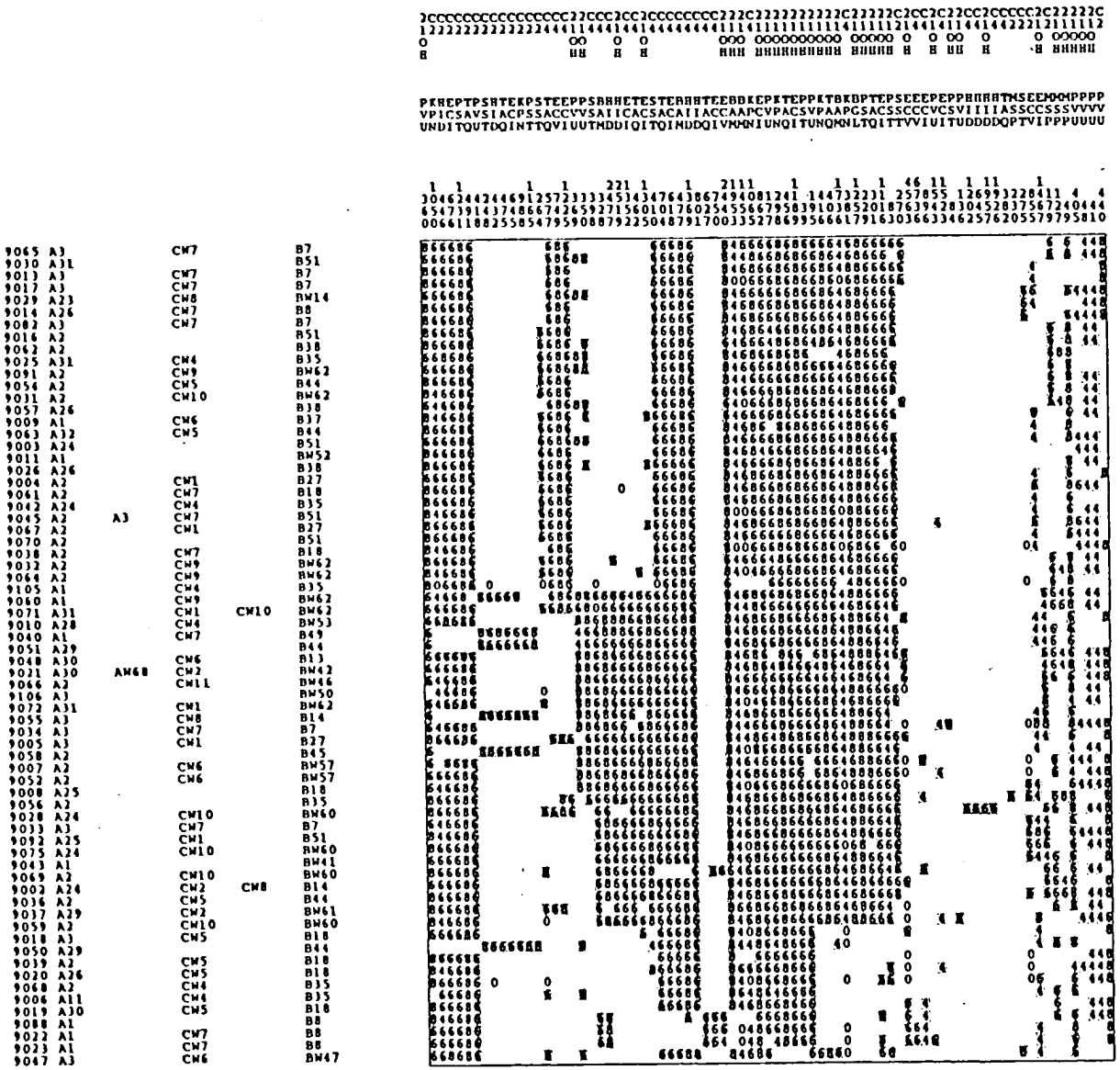
Fig. 10



Tenth International Histocompatibility Workshop
Class III loci RFLP fragments (78). Negative cluster.



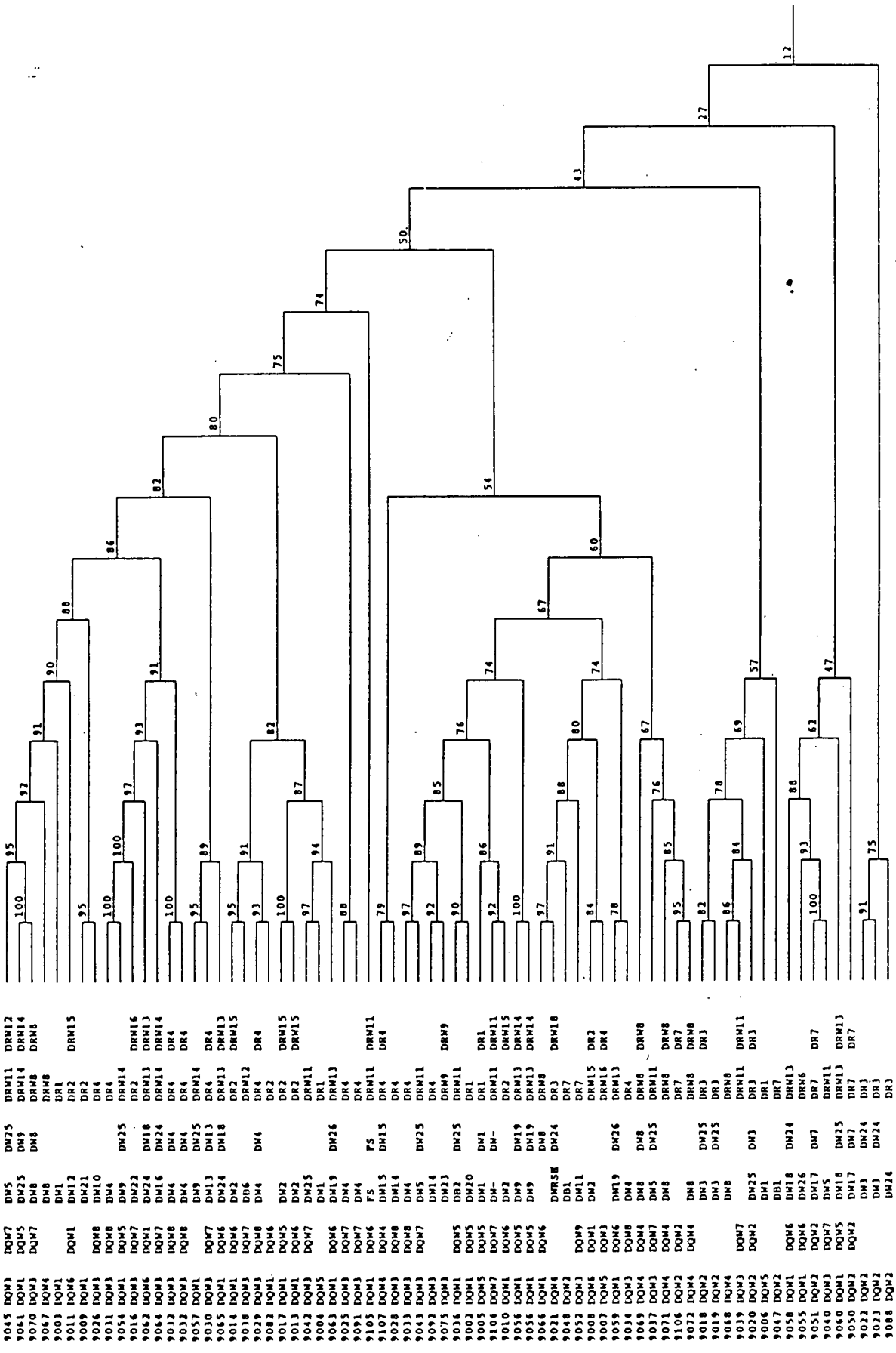
Fig. 11



Tenth International Histocompatibility Workshop
Class III loci (C2,C4,21OH) RFLP fragments (20,24,34). Positive cluster.

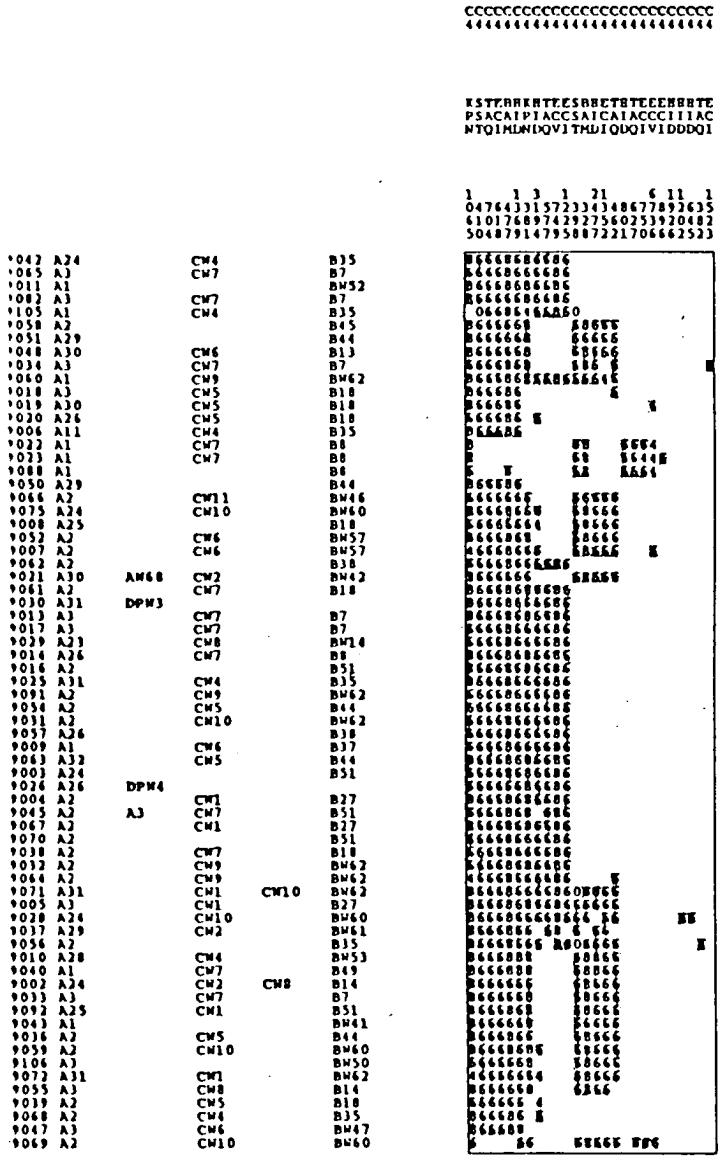


Fig. 12



Tenth International Histocompatibility Workshop
Tree analysis of cell relationships: Class III loci.

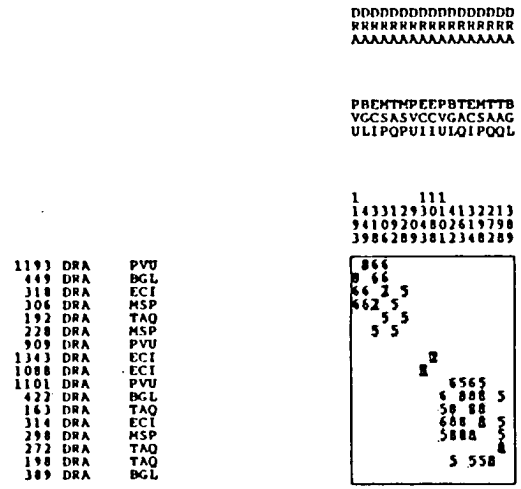
Fig. 13



Tenth International Histocompatibility Workshop
Class III C4 RFLP fragments (26). First 25 cells listed by C4 phenotype.



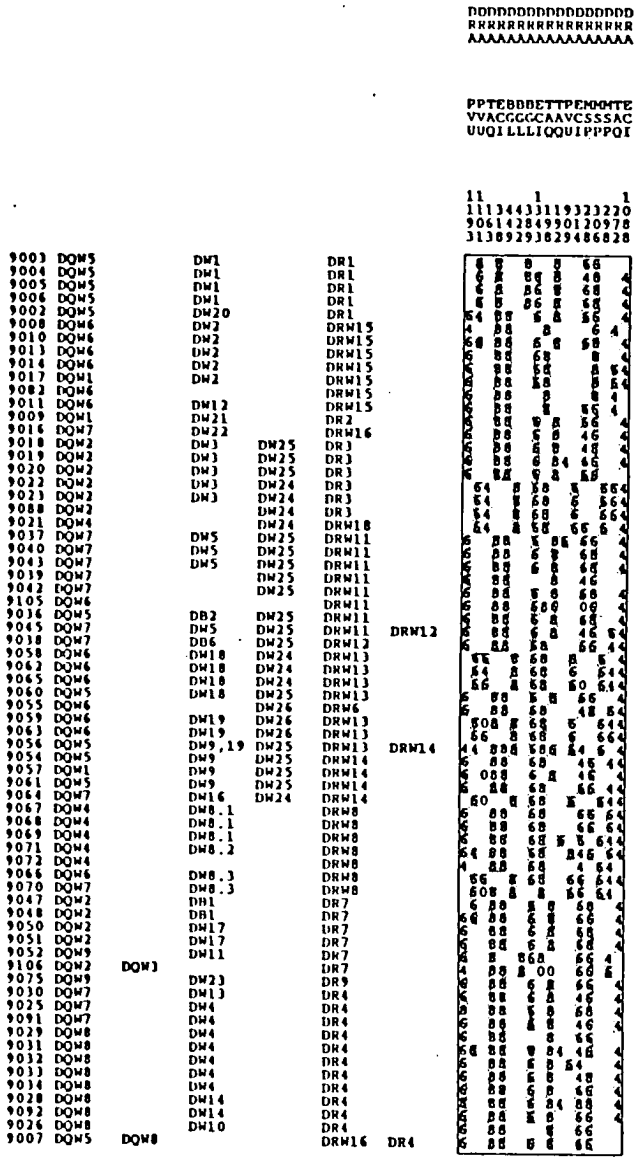
Fig. 14




Tenth International Histocompatibility Workshop
Class II DRA locus RFLP fragments (17). Fragment Cluster.

Page 1 of 1

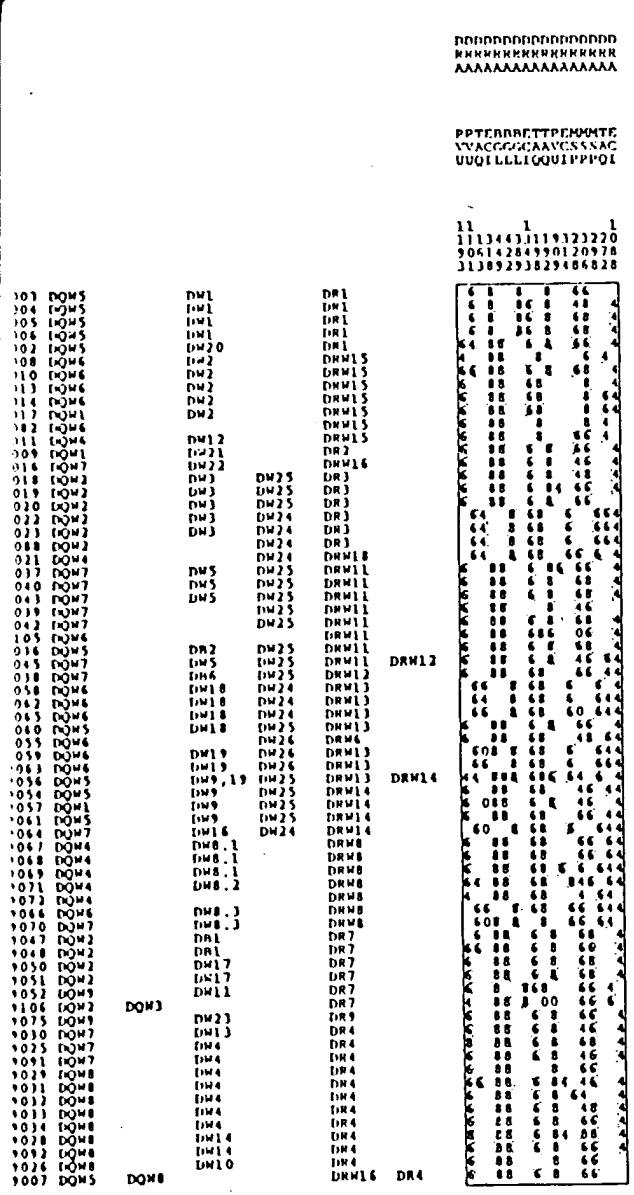
Fig. 15




Tenth International Histocompatibility Workshop
Class II DRA locus RFLP fragments (17). Negative Cluster.



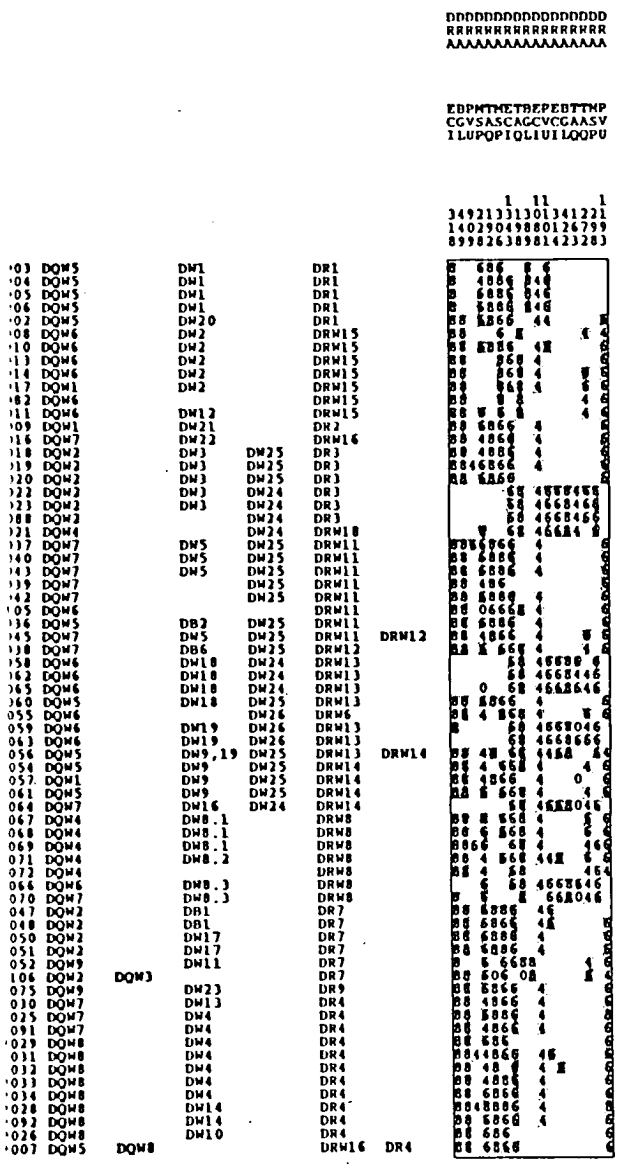
Fig. 16



Tenth International Histocompatibility Workshop
Class II DRA locus RFLP fragments (17). Negative Cluster.



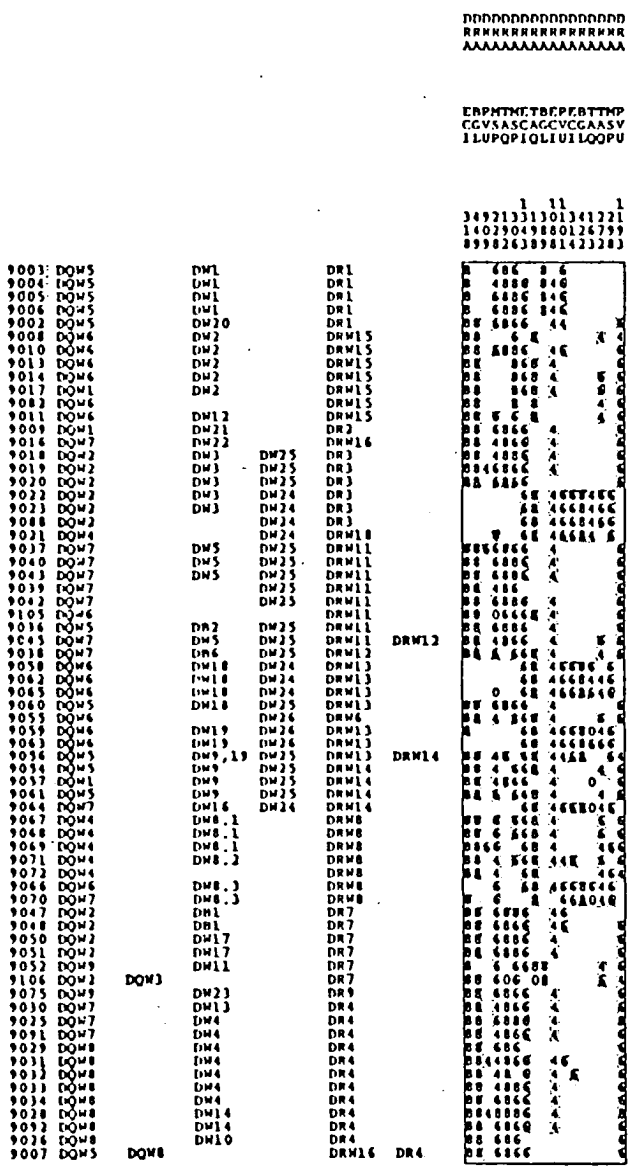
Fig. 16



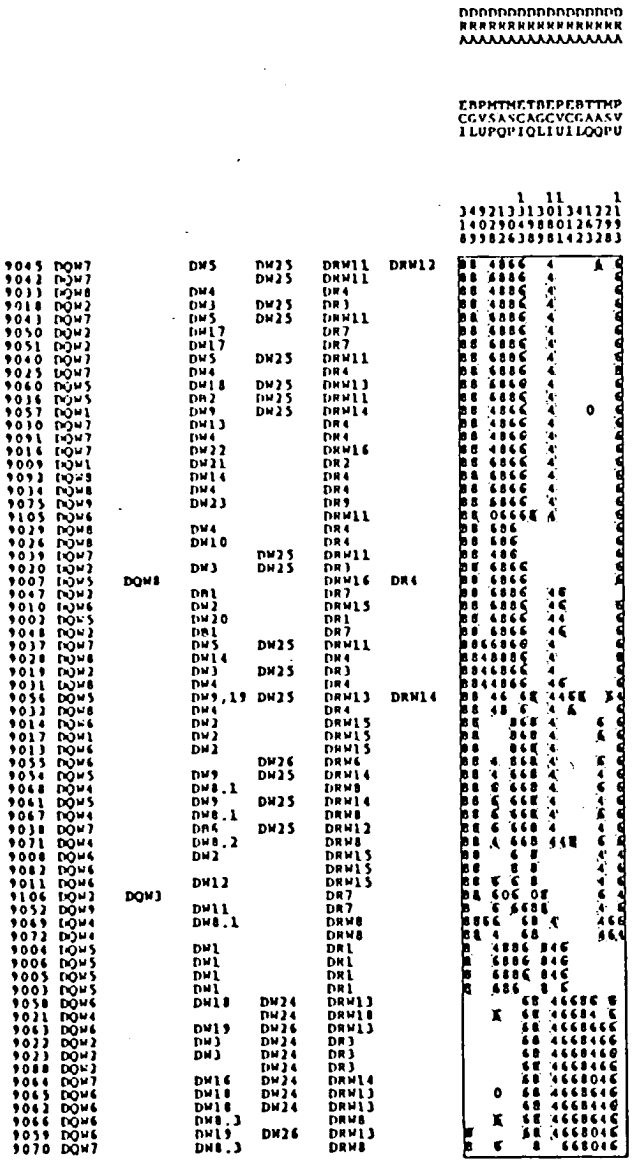
Tenth International Histocompatibility Workshop
Class II DRA locus RFLP fragments (17). Cells listed by DR specificity groups.



Fig. 17



Tenth International Histocompatibility Workshop
Class II DRA locus RFLP fragments (17). Cells listed by DR specificity groups.



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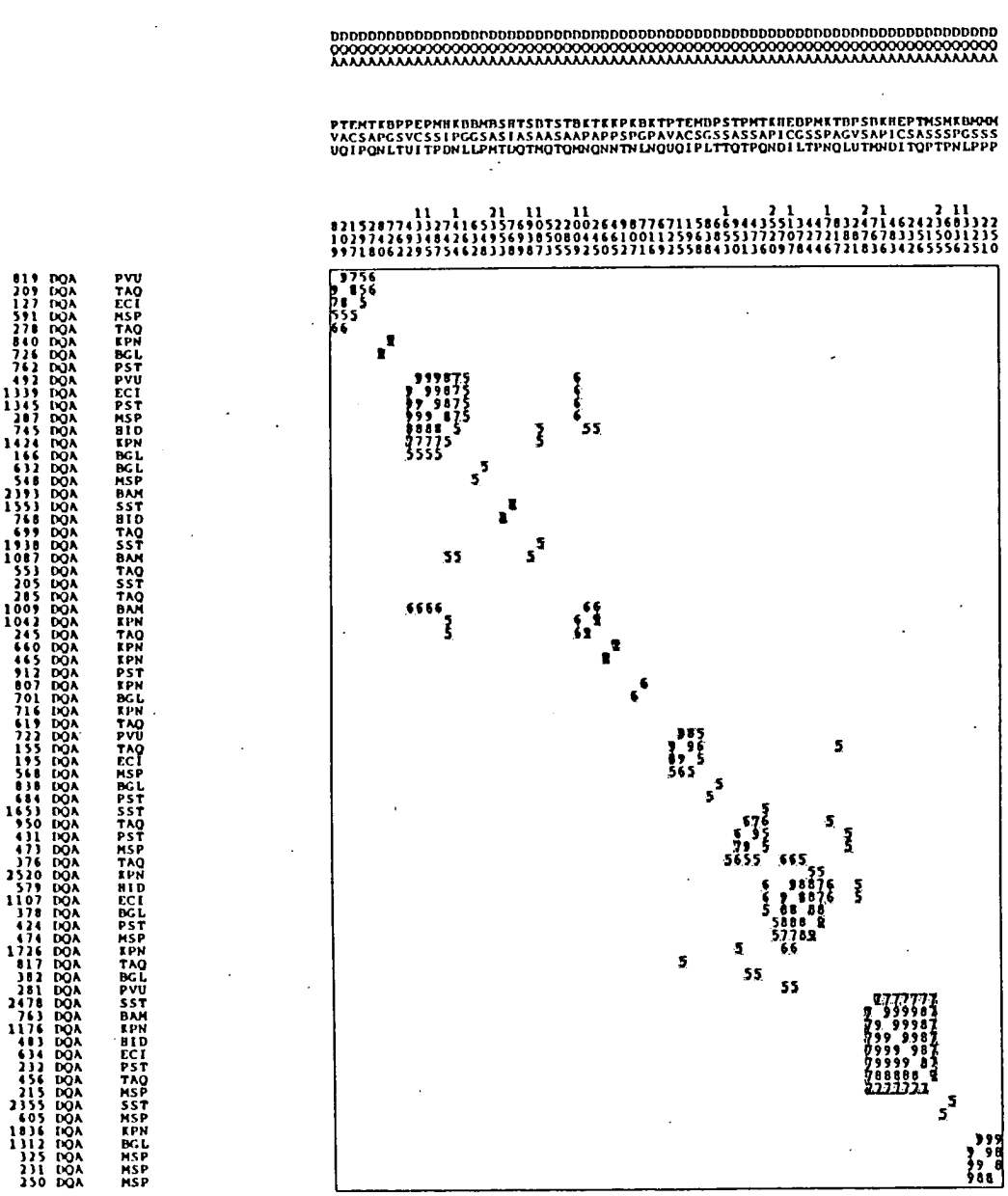
Class II DRA locus RFLP fragments (17). Cells listed by Tree relationships.



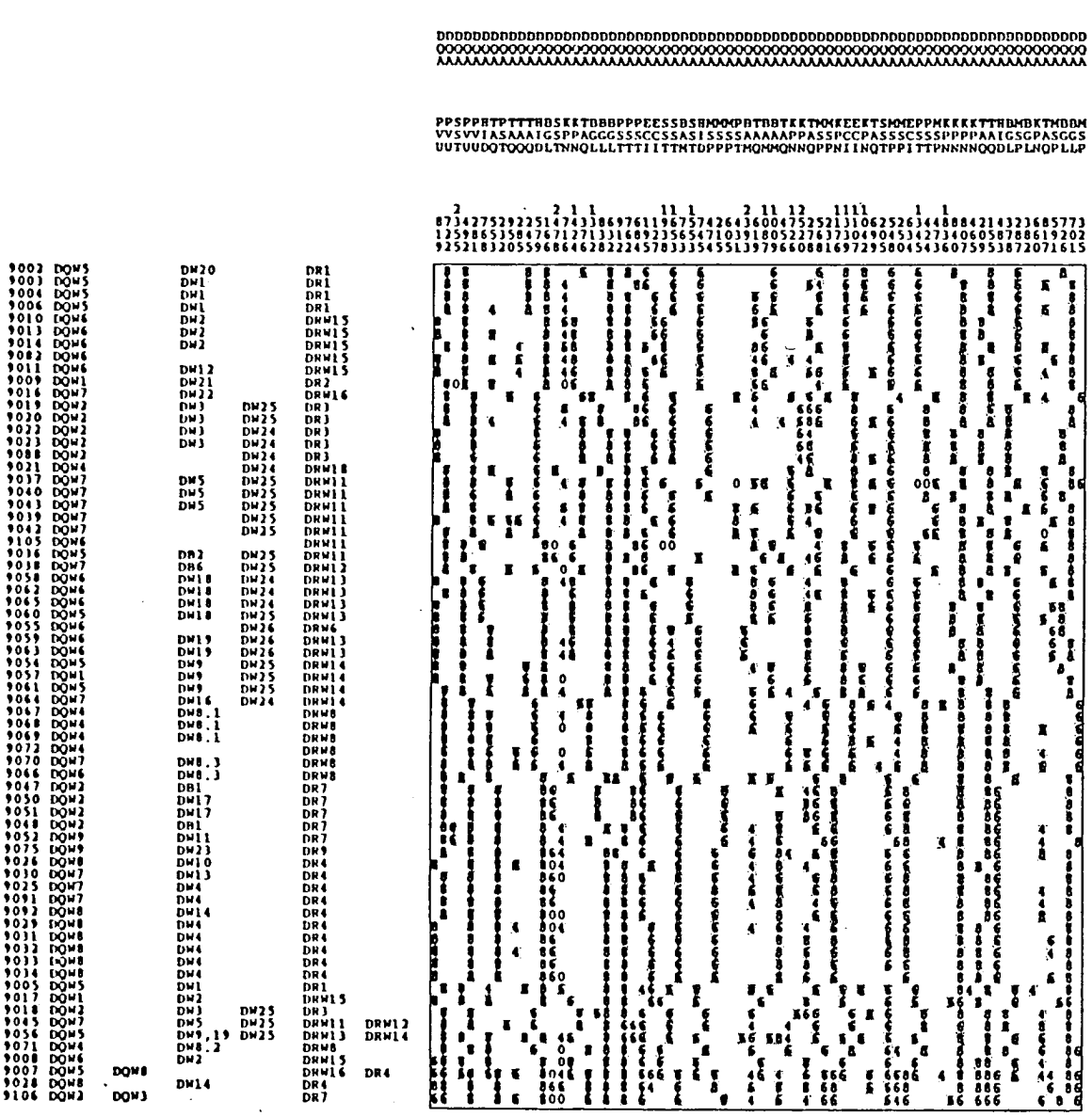
Fig. 18



Tenth International Histocompatibility Workshop
Class II DQA,DXA loci RFLP fragments (72). Fragment cluster.



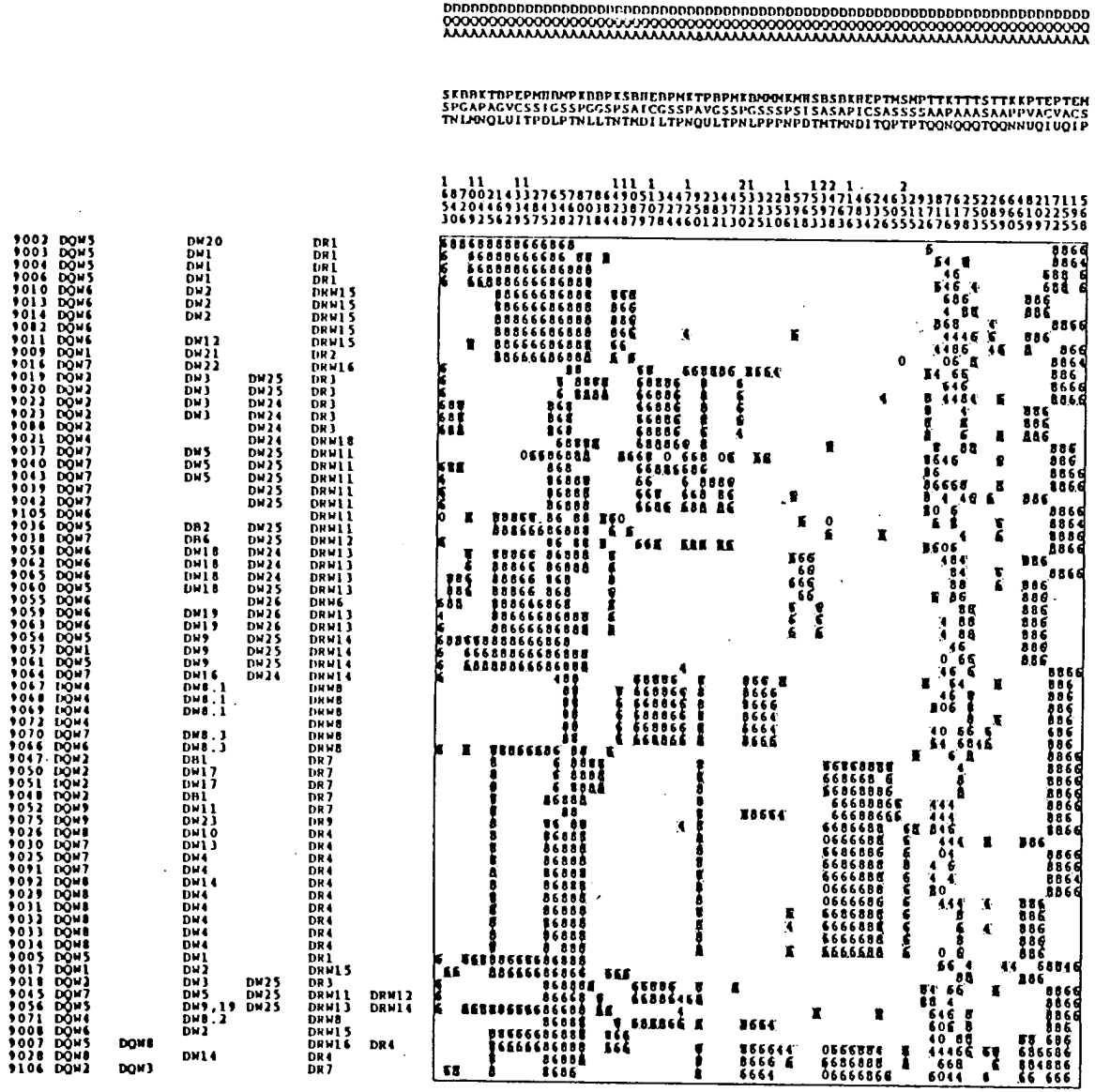
Fig. 19



Tenth International Histocompatibility Workshop
Class II DQA locus RFLP fragments (72). Negative cluster.



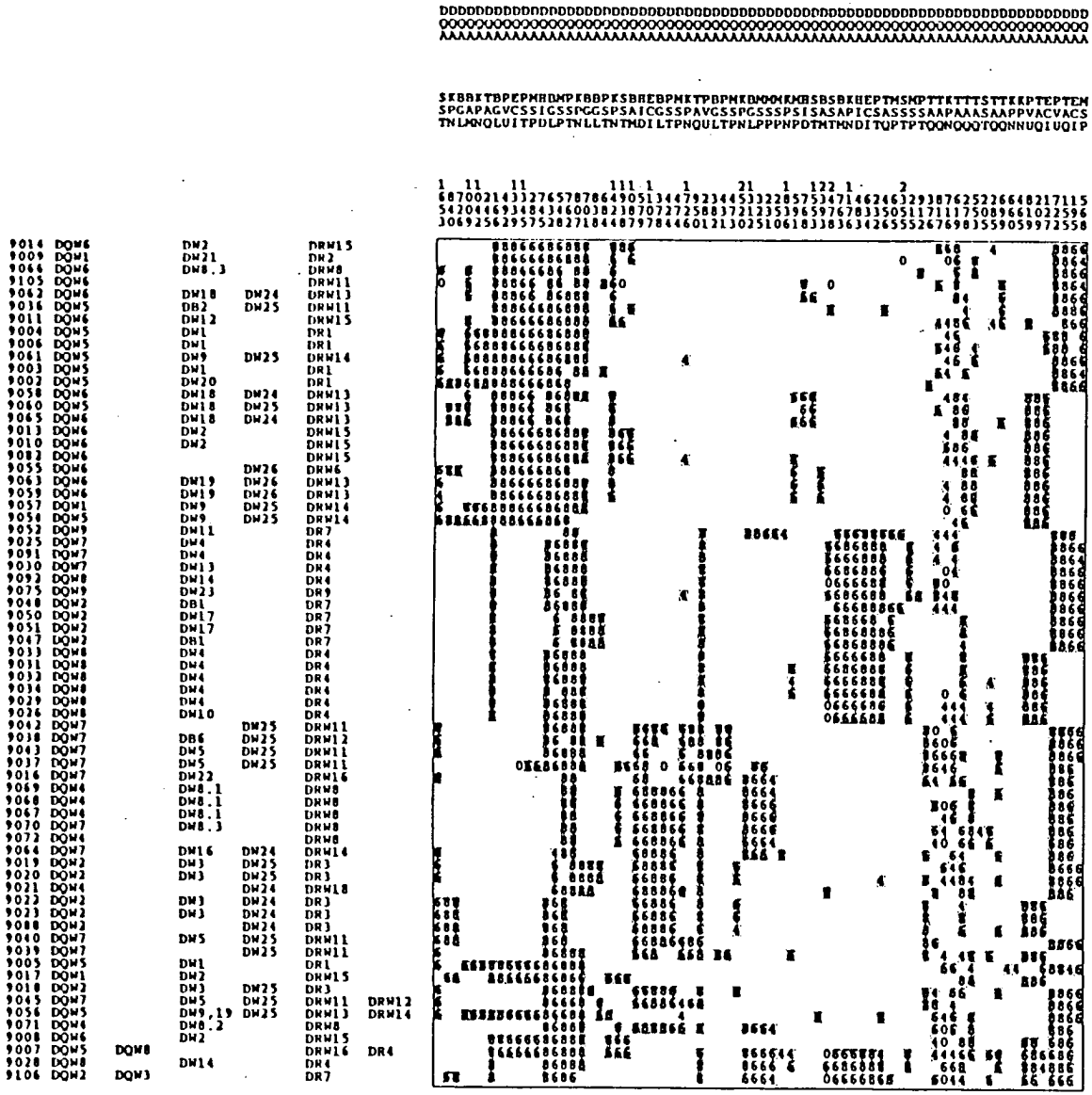
Fig. 20



Tenth International Histocompatibility Workshop
Class II DQA,DXA loci RFLP fragments (72). Cells listed by DR,Dw specificity groups.



Fig. 21



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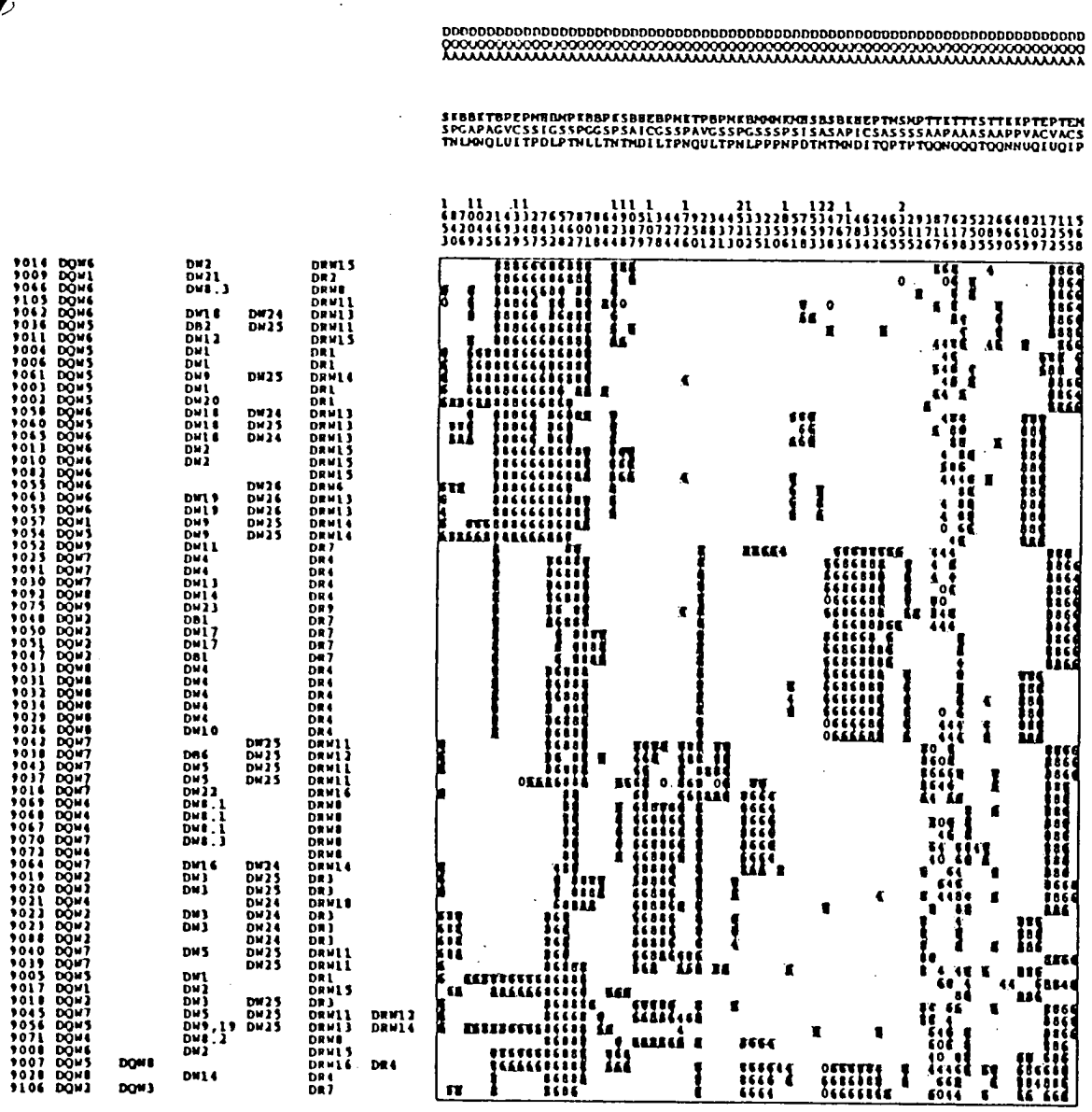
Class II DQA,DXA loci RFLP fragments (72). Cells listed by Tree relationships (60 homozygous cells).



Fig. 22

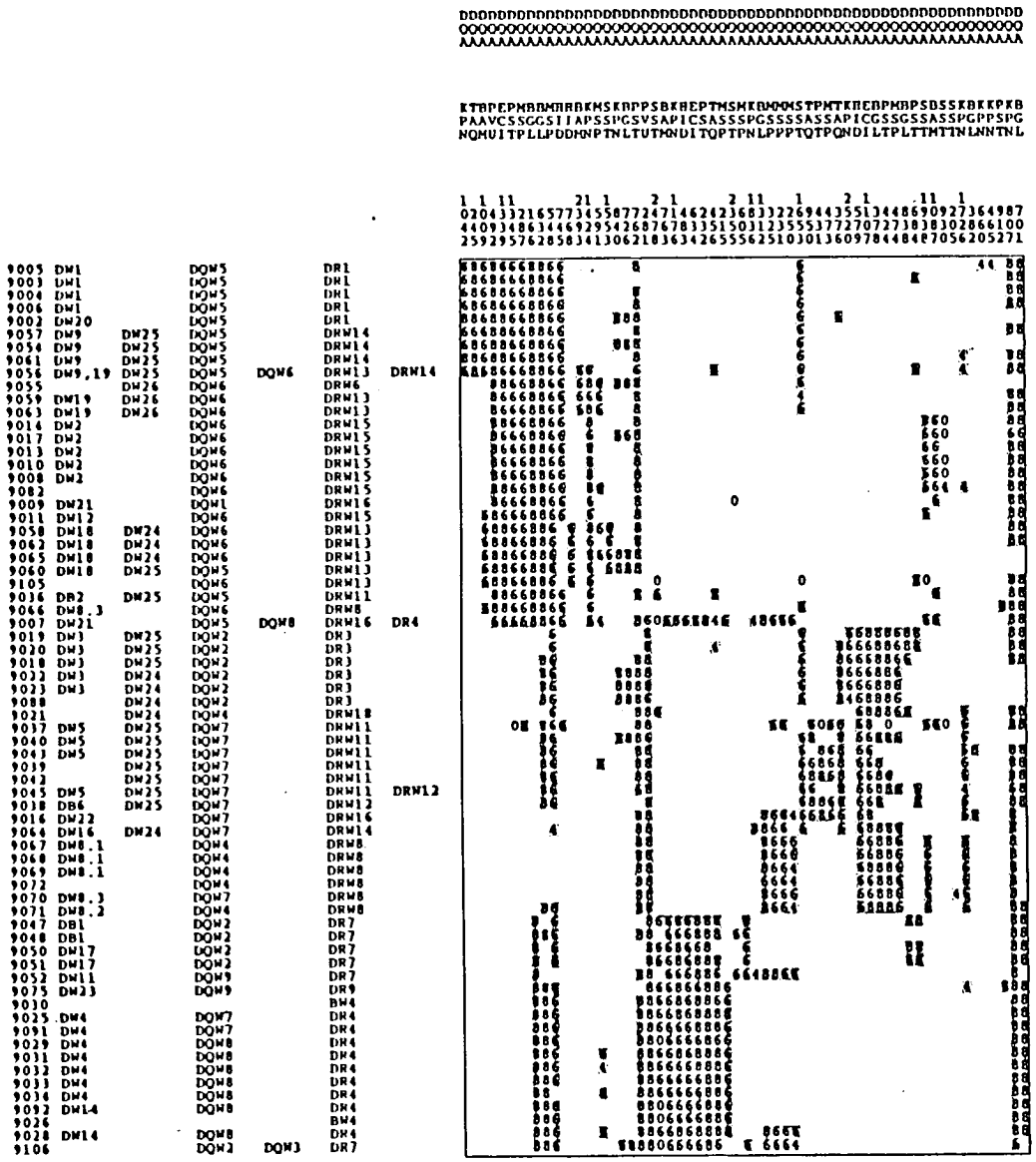


Tenth International Histocompatibility Workshop

Class II DQA,DXA loci RFLP fragments (72). Cells listed by Tree relationships (60 homozygous cells).



Fig. 22



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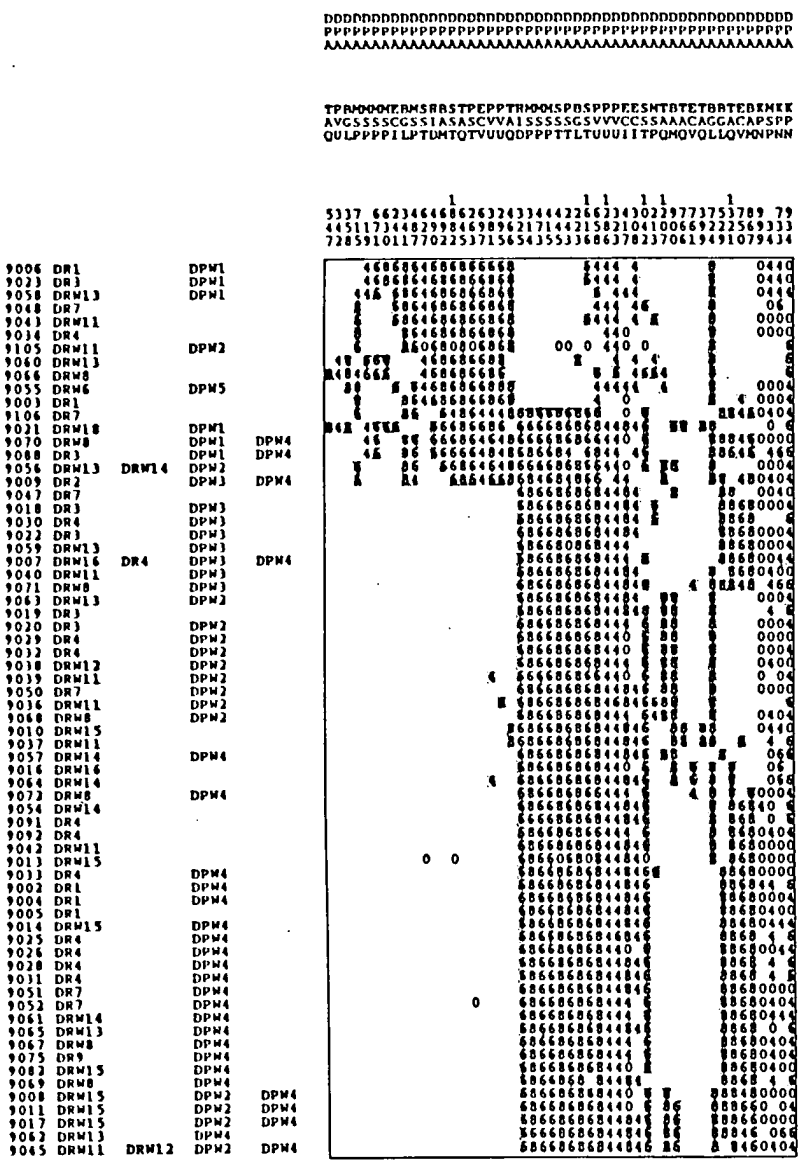
Class II DQA1 locus RFLP fragments (59). Cells grouped according to available DQA1 sequence type.



Fig. 23



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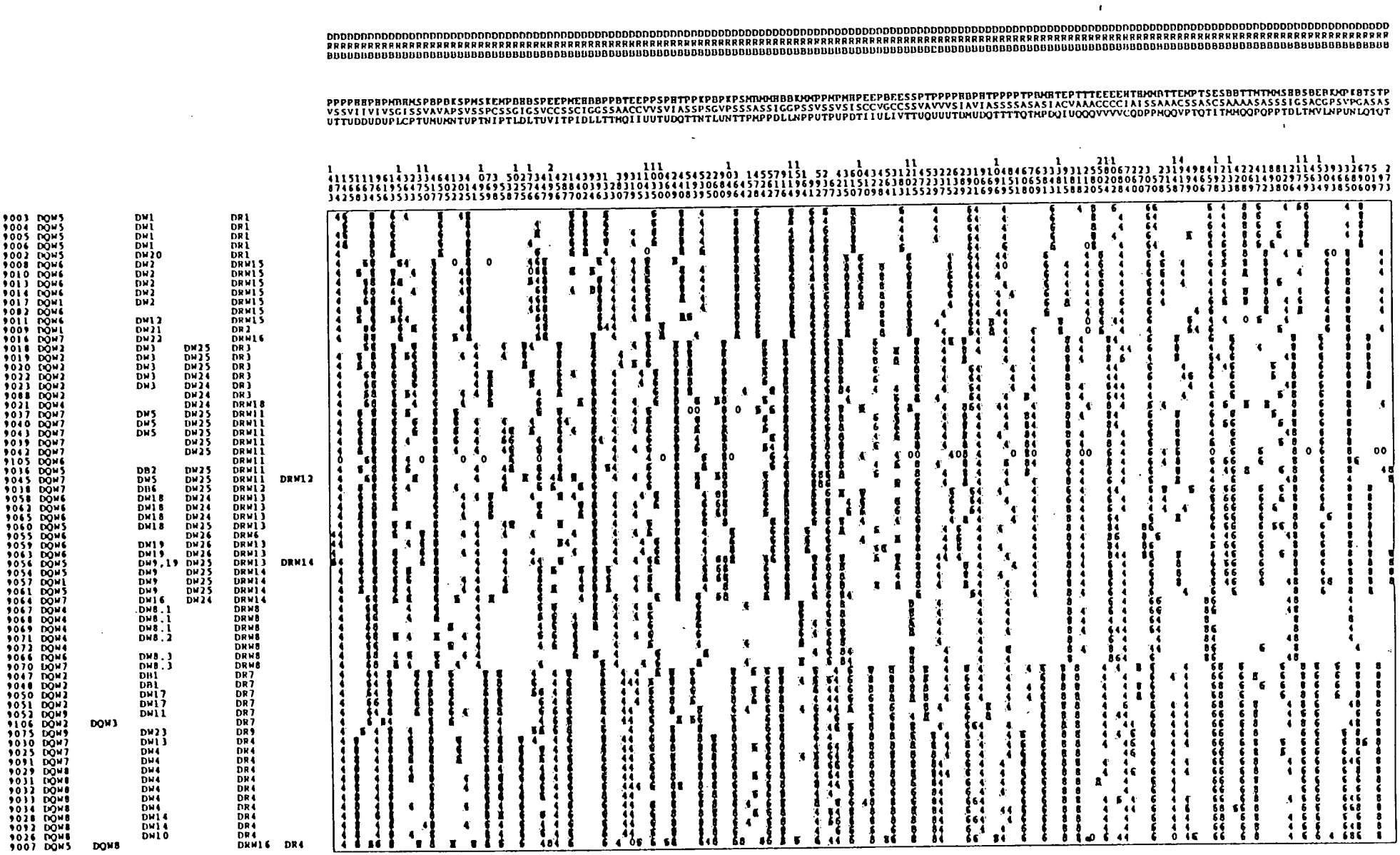
Class II DPA RFLP fragments (49). W/S cells listed to show fragment patterns.



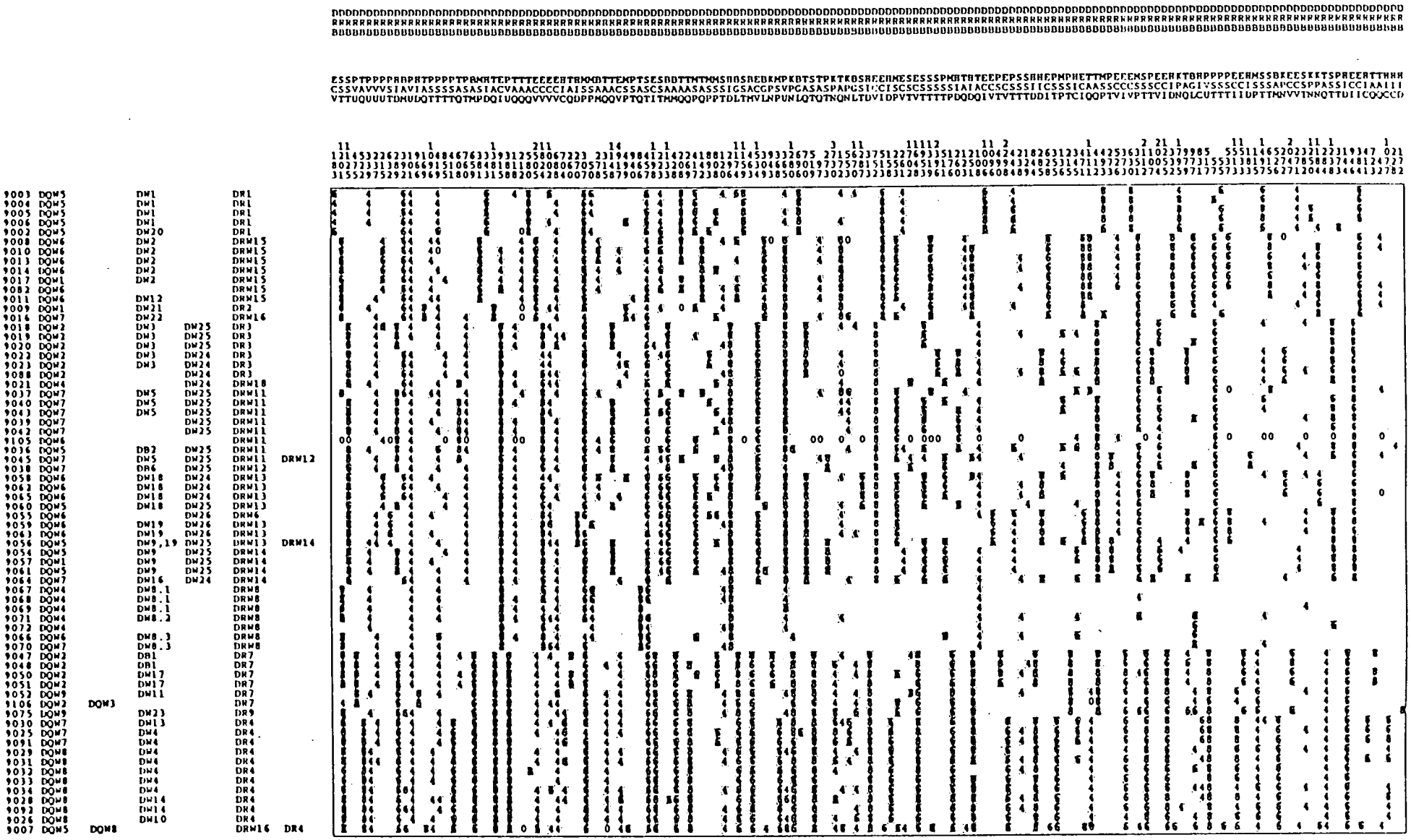
Fig. 24



Tenth International Histocompatibility Workshop
Class II DRB loci RFLP fragments (238). Negative cluster.



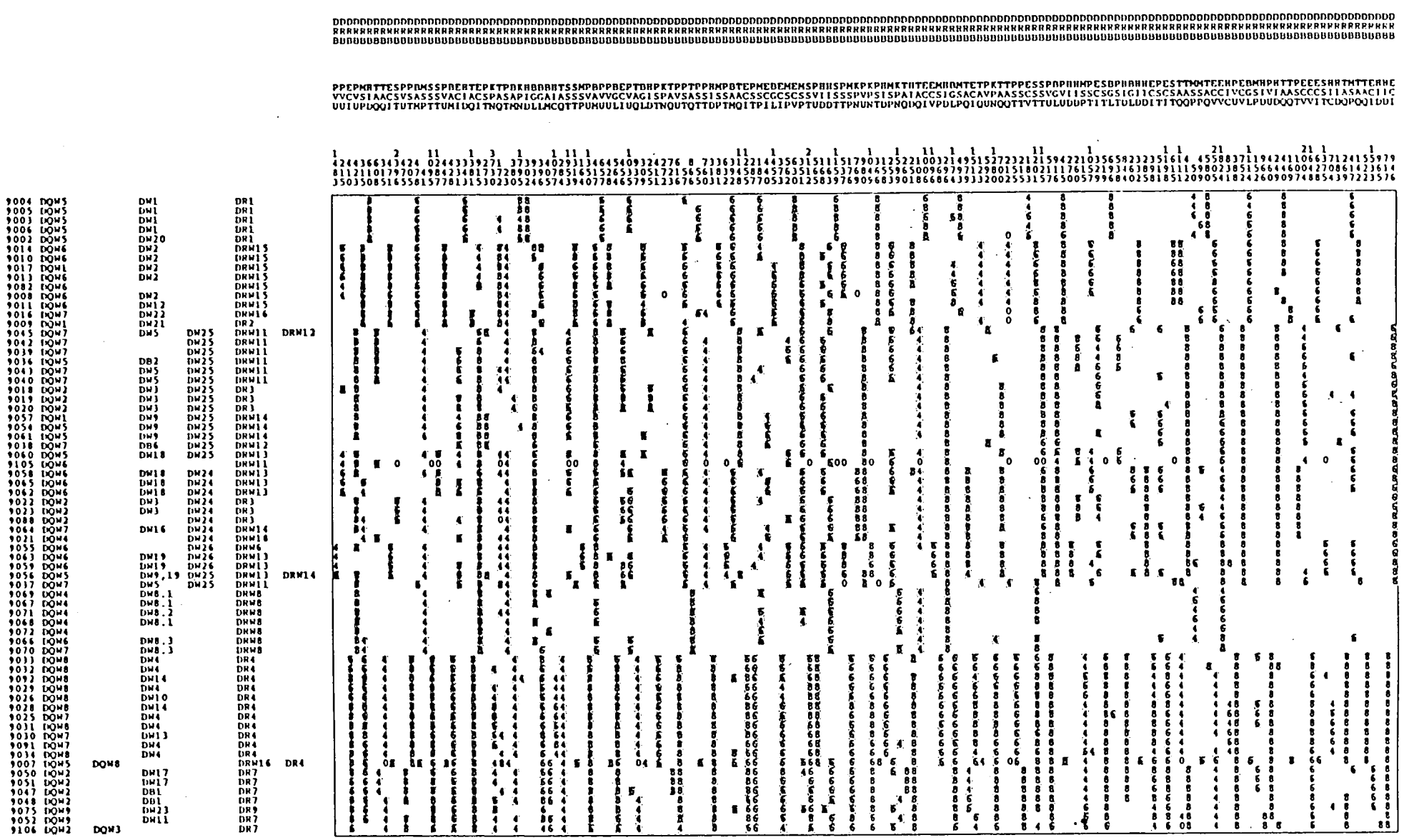
Fig. 25a



Tenth International Histocompatibility Workshop
Class II DRB loci RFLP fragments (238). Negative cluster.



Fig. 25b



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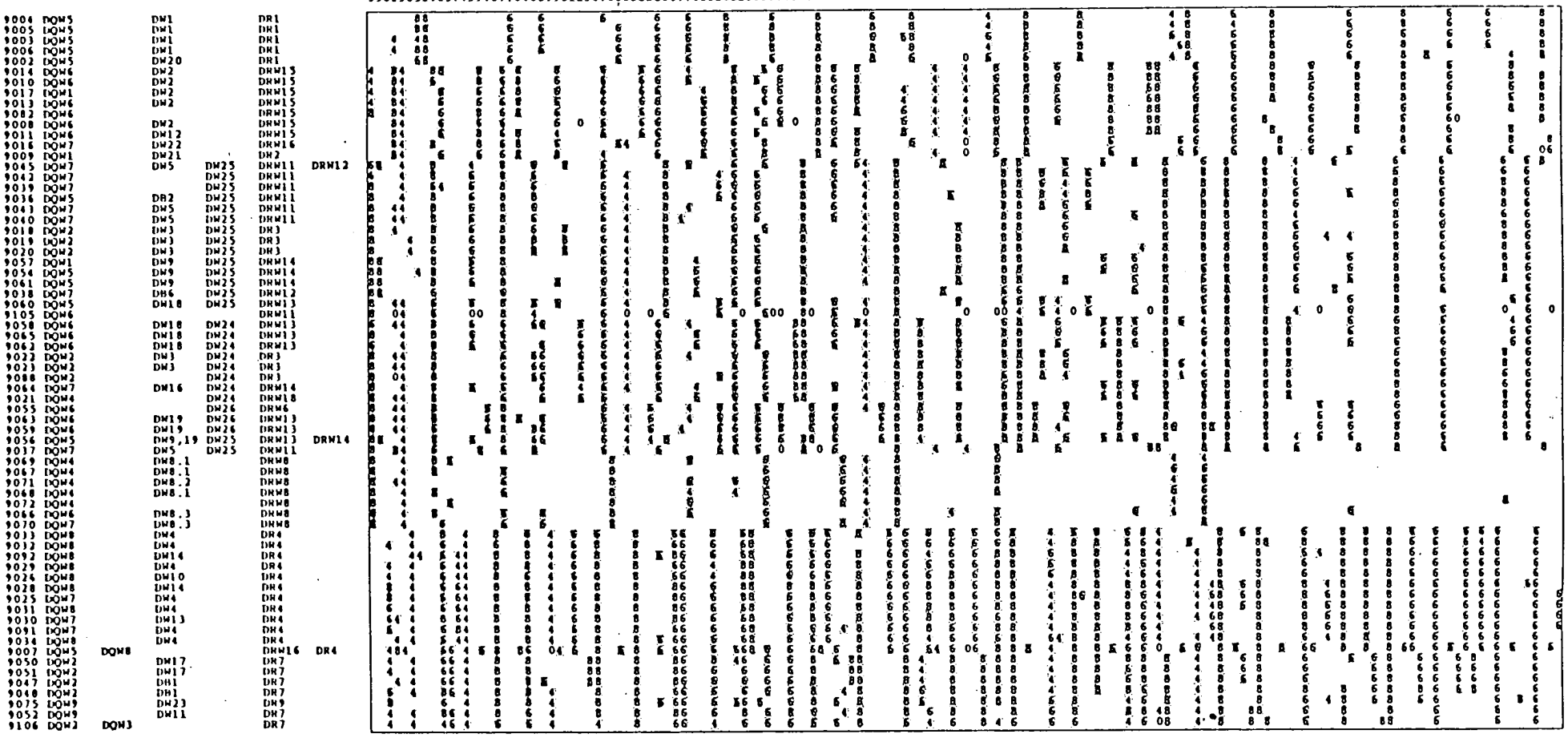
Tenth International Histocompatibility Workshop
Class II DRB loci RFLP fragments (176). Negative cluster.



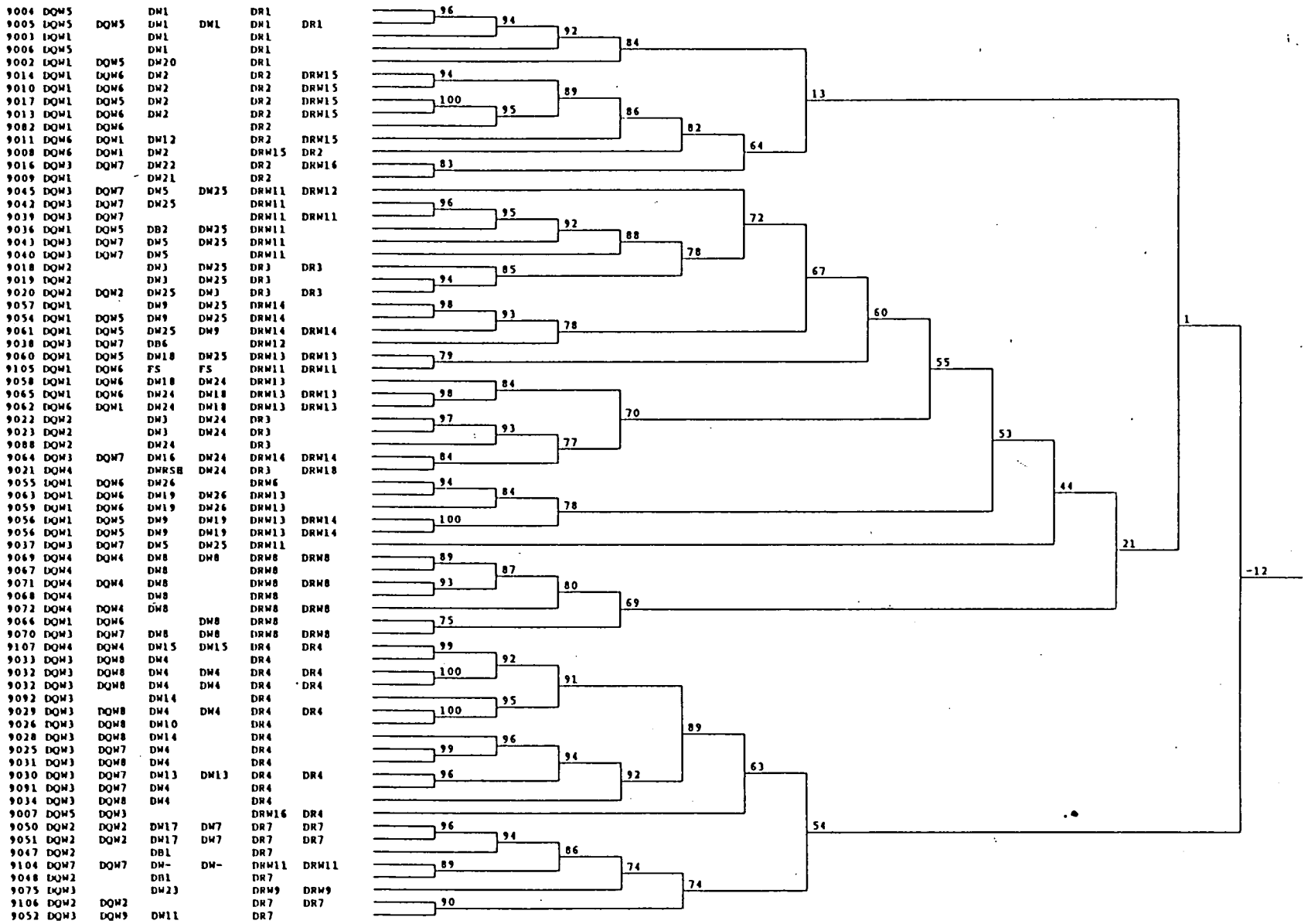
Fig. 26a



Tenth International Histocompatibility Workshop
Class II DRB loci RFLP fragments (176). Negative cluster.

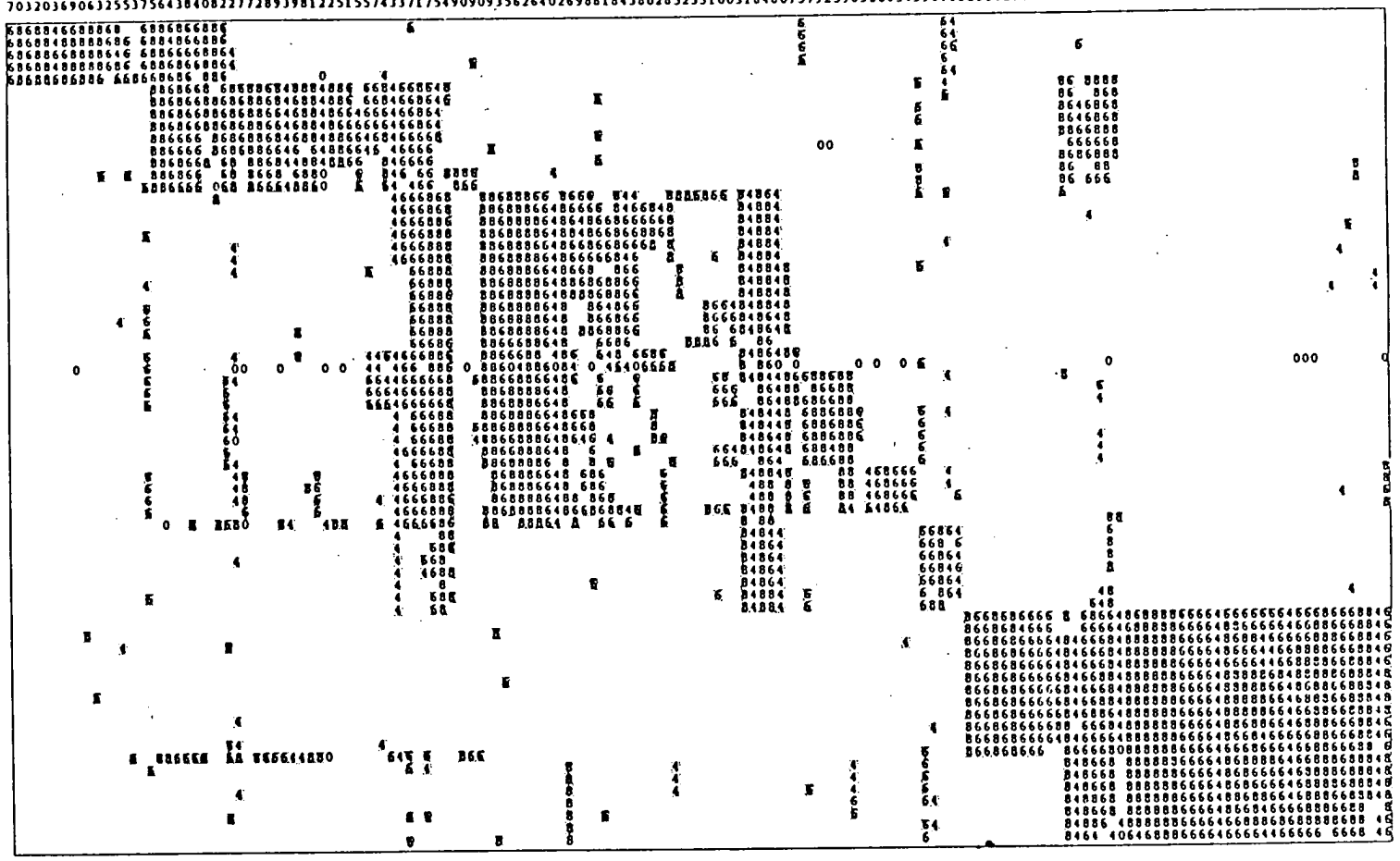


Fig. 26b




Tenth International Histocompatibility Workshop
Tree analysis of cell relationships: DRB loci RFLP fragments (176).

Fig. 27



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Class II DRB loci RFLP fragments (176). Cells listed by Tree relationships.

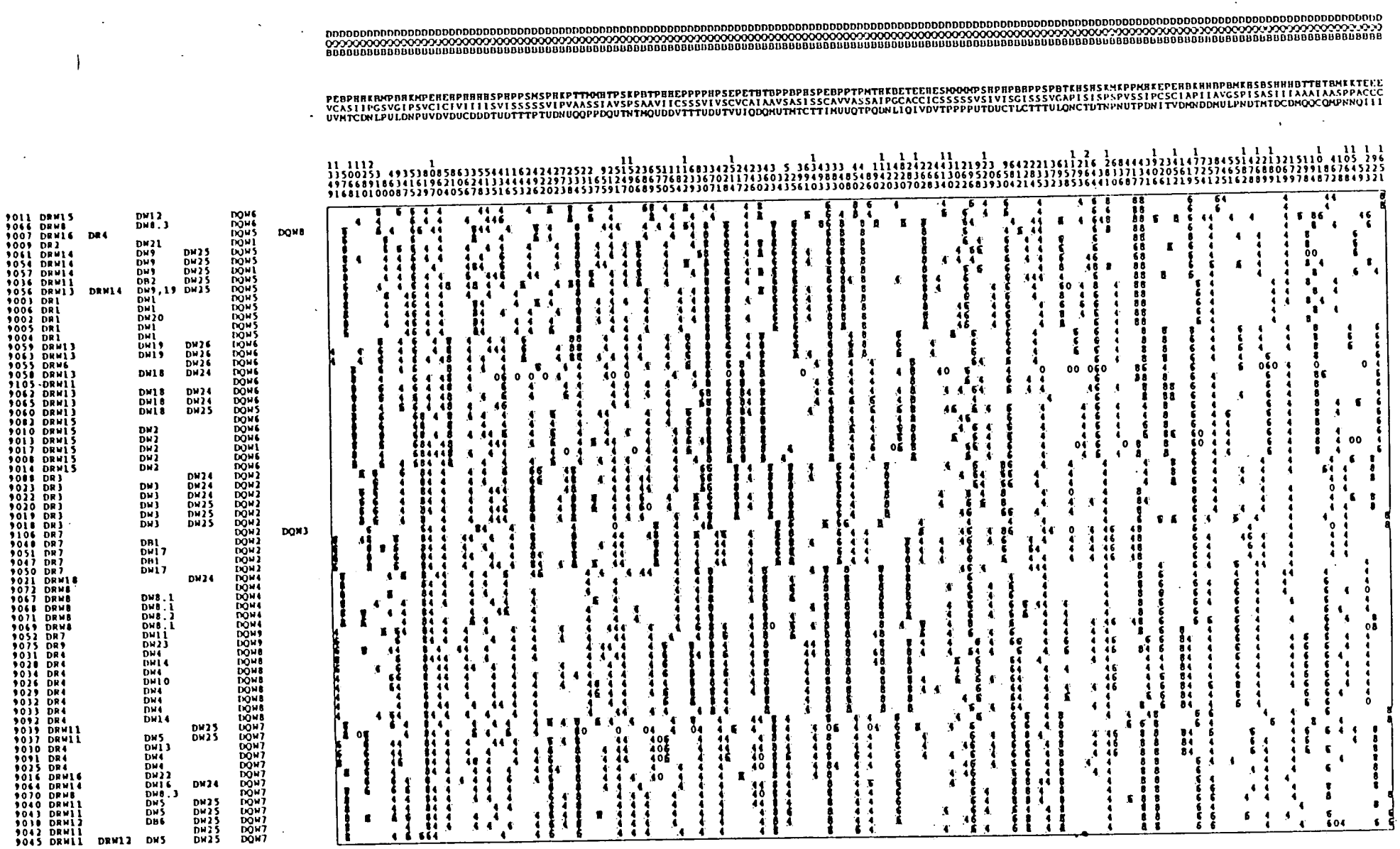


Fig. 28a

Tenth International Histocompatibility Workshop
Class II DRB loci RFLP fragments (176). Cells listed by Tree relationships.



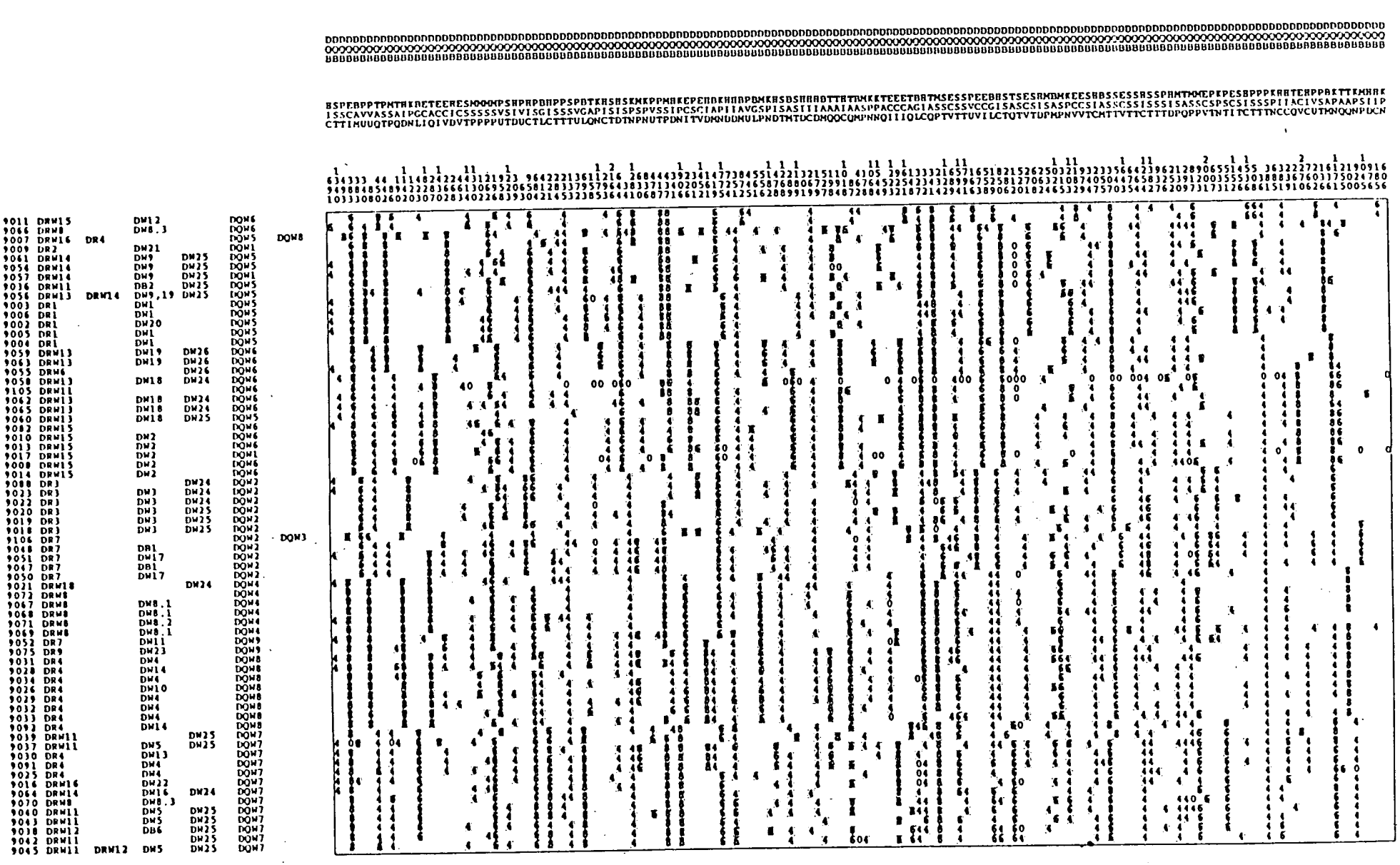
Fig. 28b



Tenth International Histocompatibility Workshop
Class II DQB loci RFLP fragments (225). Negative cluster. Cells listed by Tree relationships.



Fig. 29a

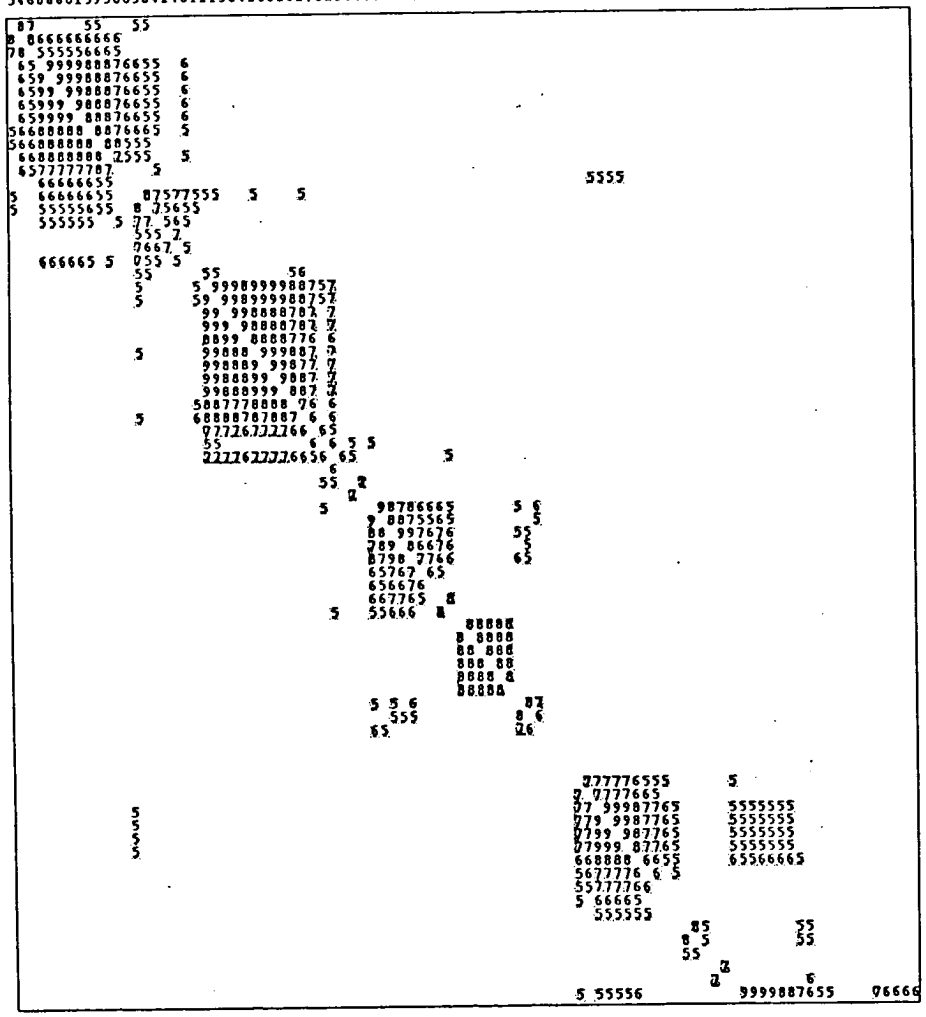


Tenth International Histocompatibility Workshop

Class II DQB loci RFLP fragments (225). Negative cluster. Cells listed by Tree relationships.



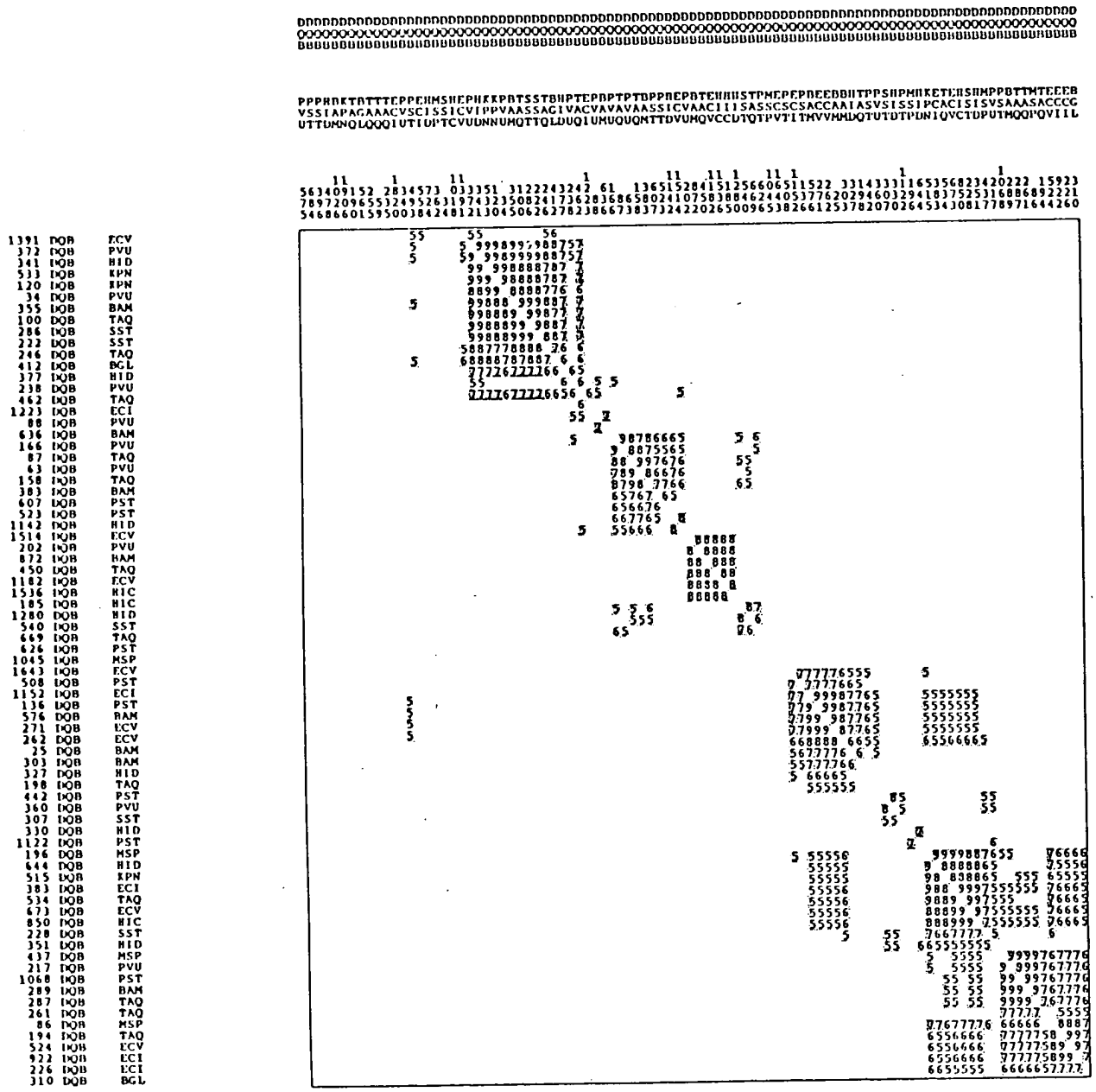
Fig. 29b



Tenth International Histocompatibility Workshop
Class II DQB loci RFLP fragments (94). Fragment x fragment cluster.



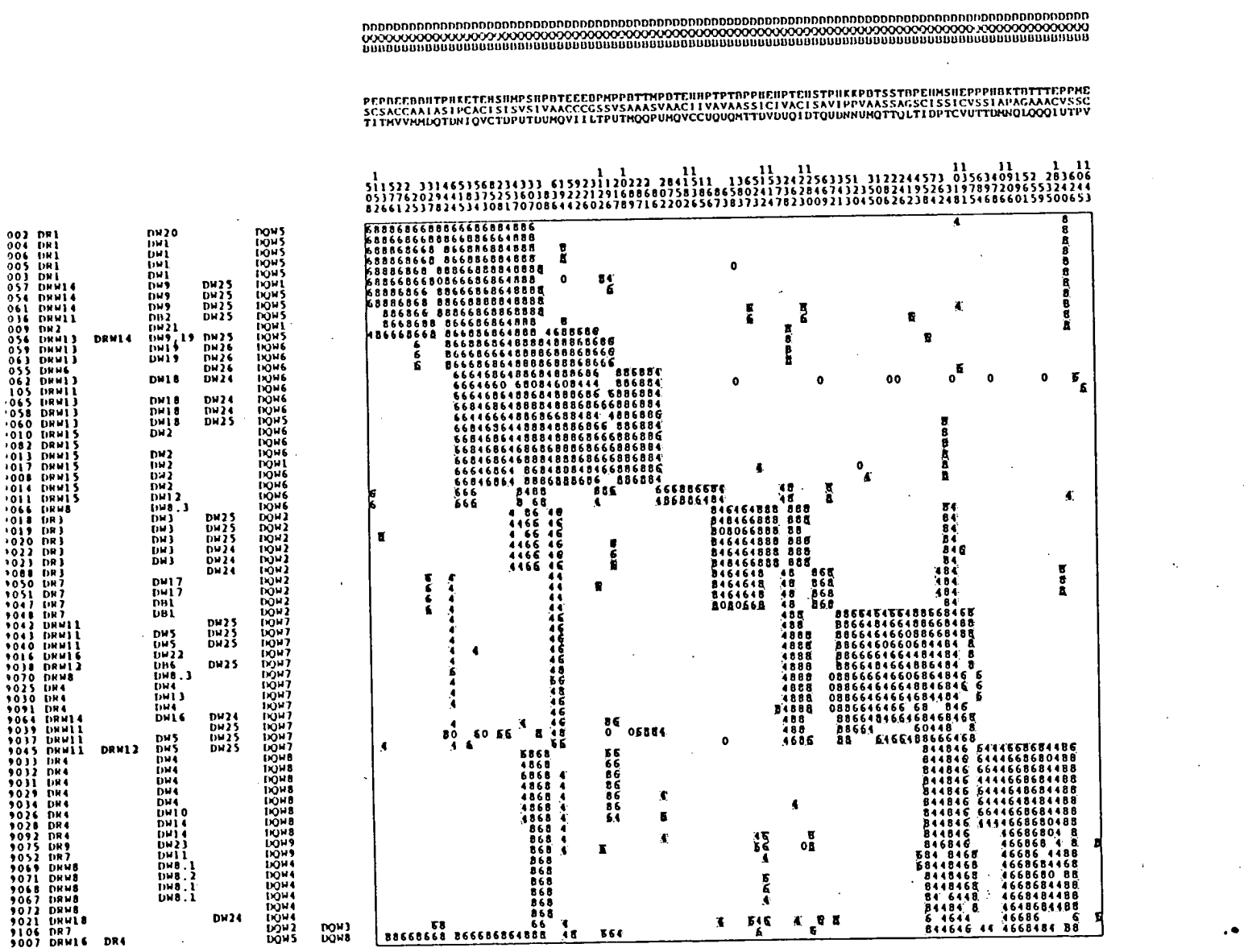
Fig. 30a



Tenth International Histocompatibility Workshop
Class II DQB loci RFLP fragments (94). Fragment x fragment cluster.



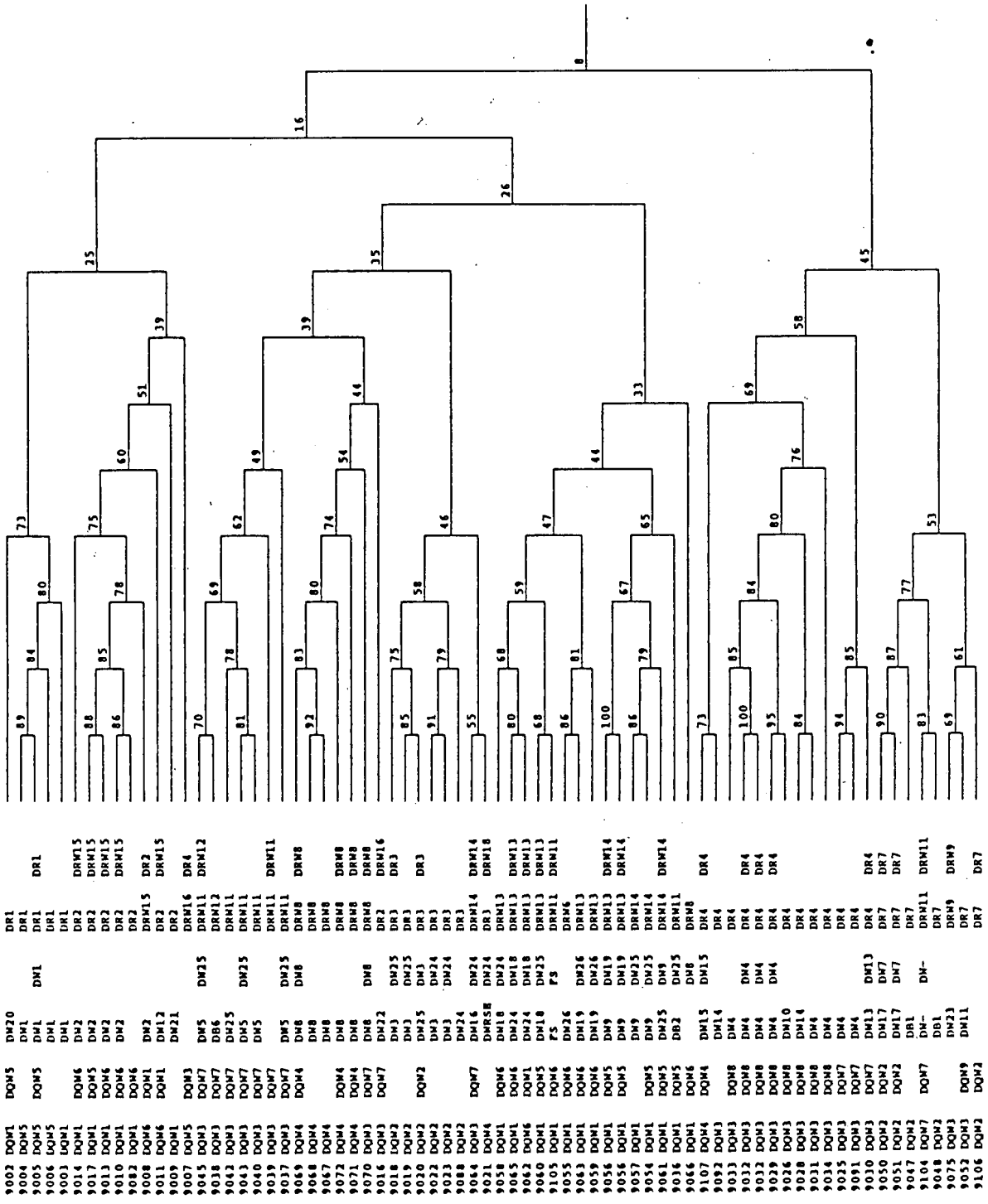
Fig. 30b



Tenth International Histocompatibility Workshop
Class II DQB loci RFLP fragments (94). Cell listing based on Tree relationships.

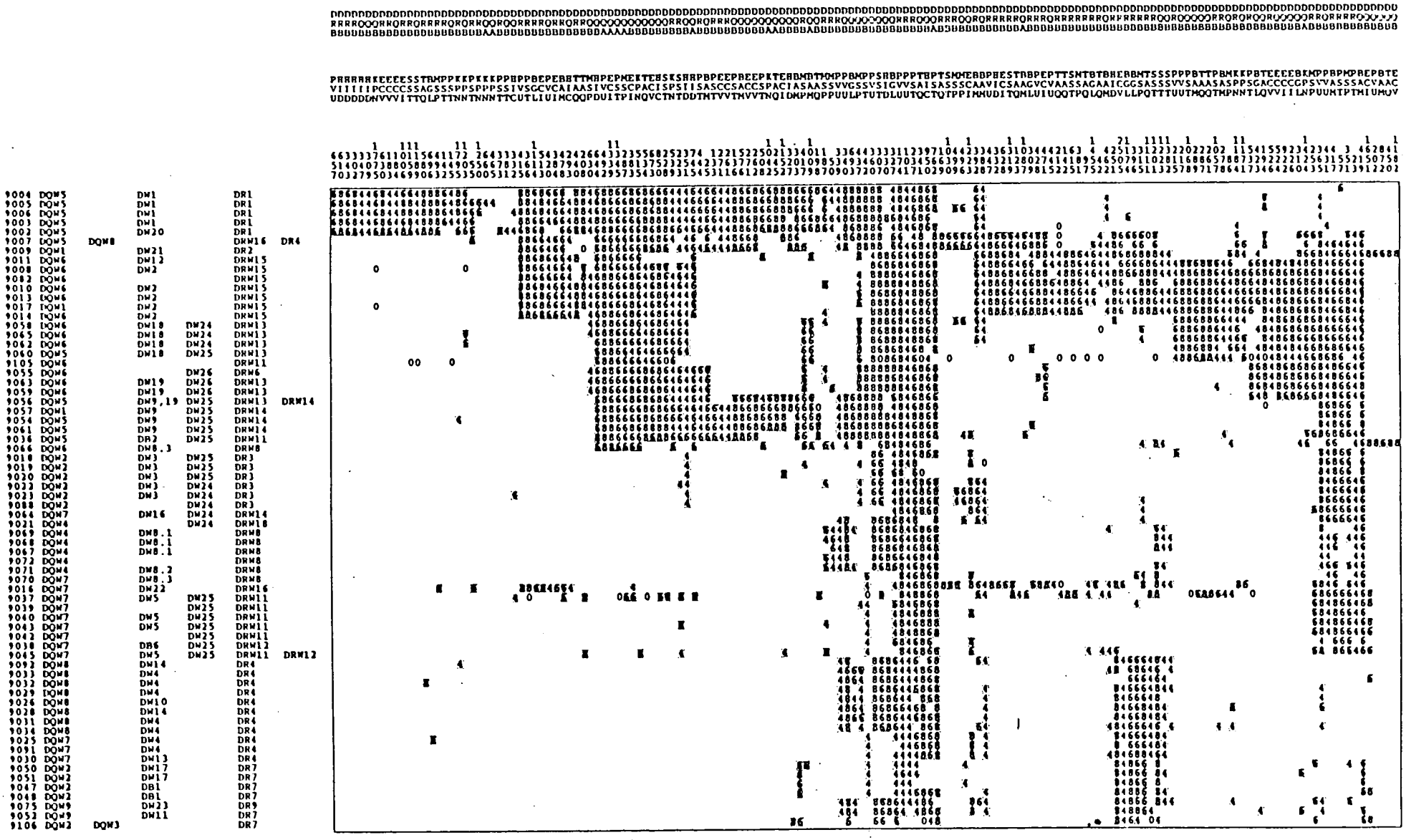


Fig. 31



Tenth International Histocompatibility Workshop
Tree analysis of cell relationships: DRB,DQA,DQB loci RFLP fragments (537).

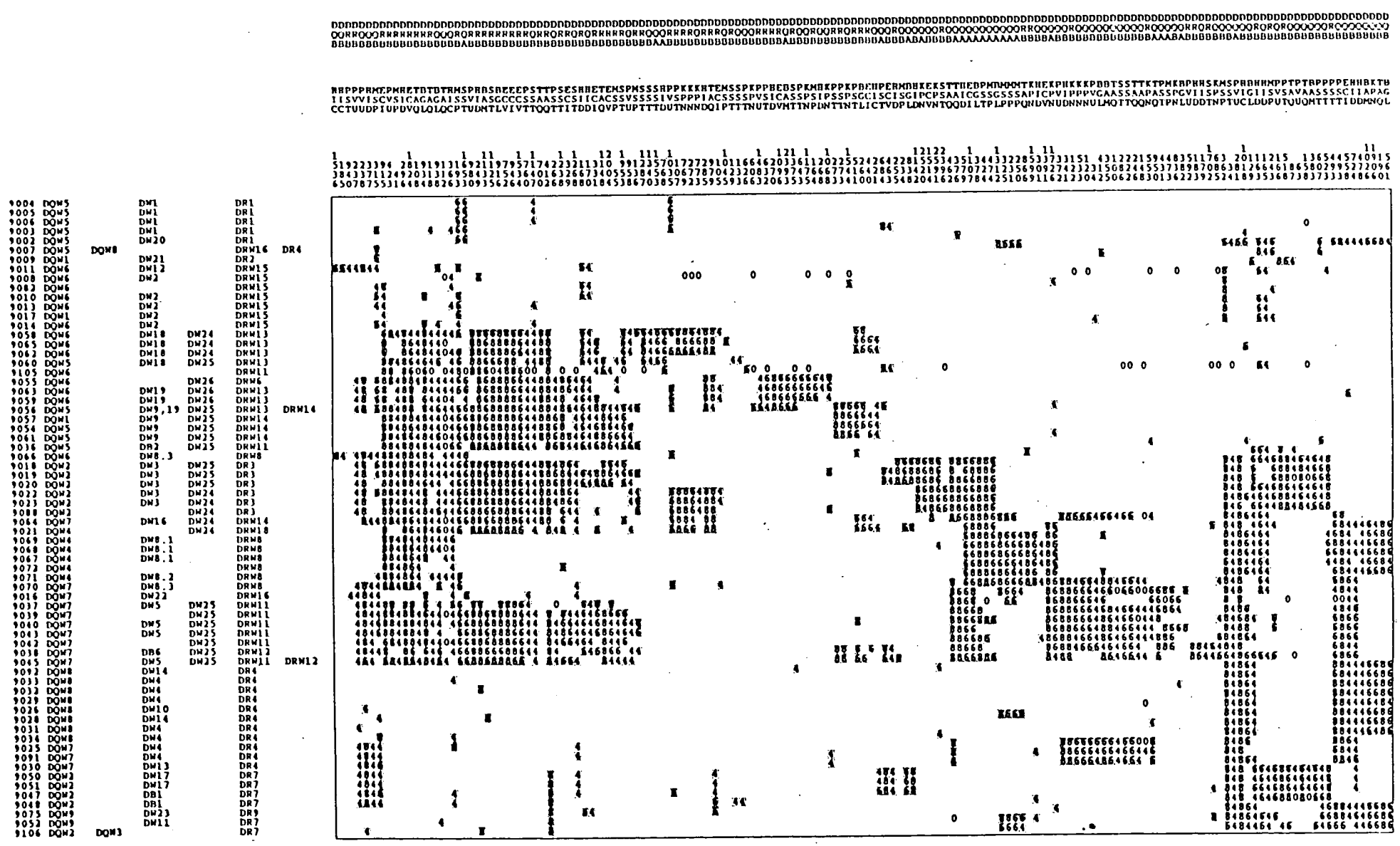
Fig. 32




Tenth International Histocompatibility Workshop
Class II DRB,DQA,DQB loci RFLP fragments (536). Cells listed by Tree relationships.



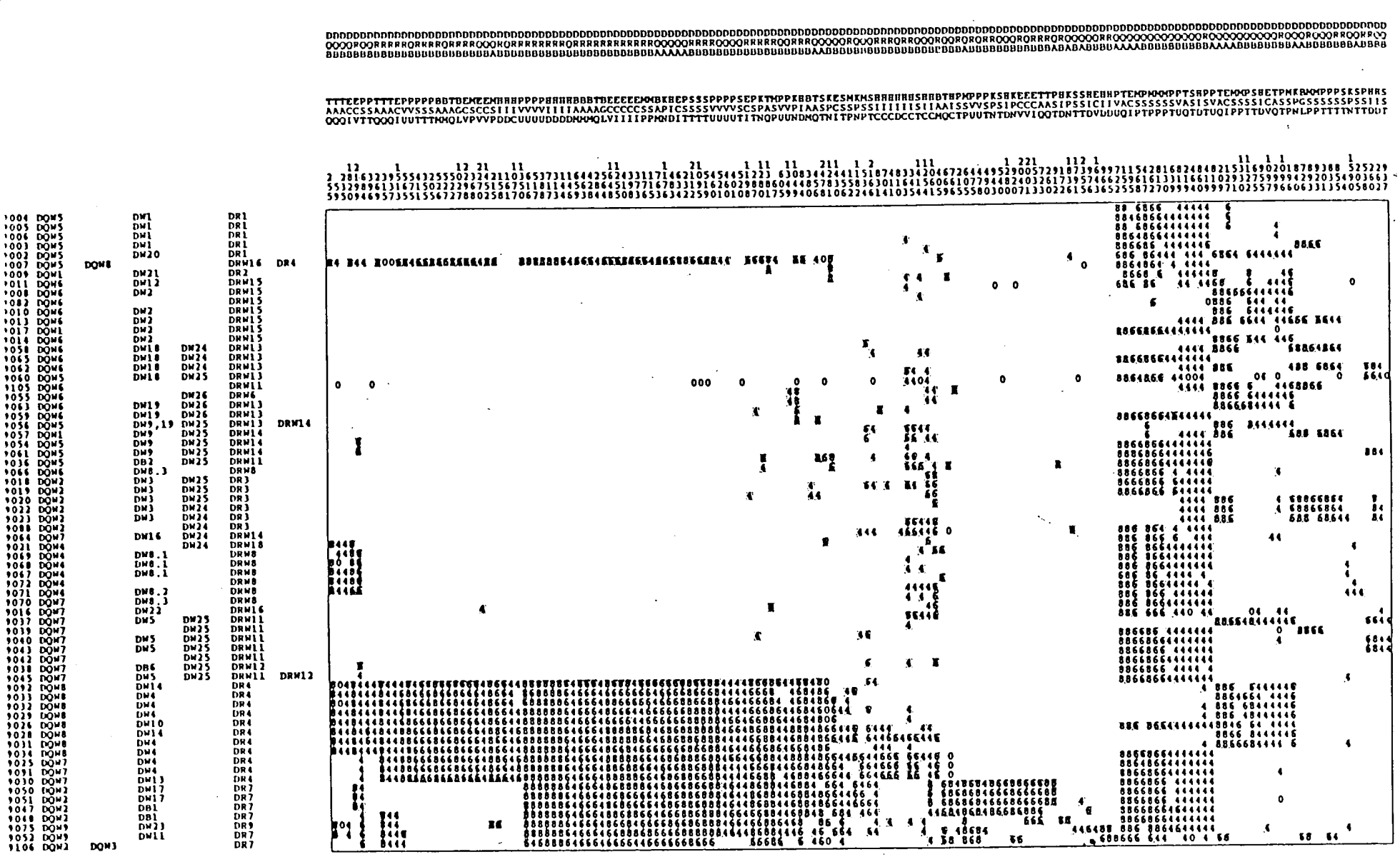
Fig. 33a



Tenth International Histocompatibility Workshop
Class II DRB,DQA,DQB loci RFLP fragments (536). Cells listed by Tree relationships.



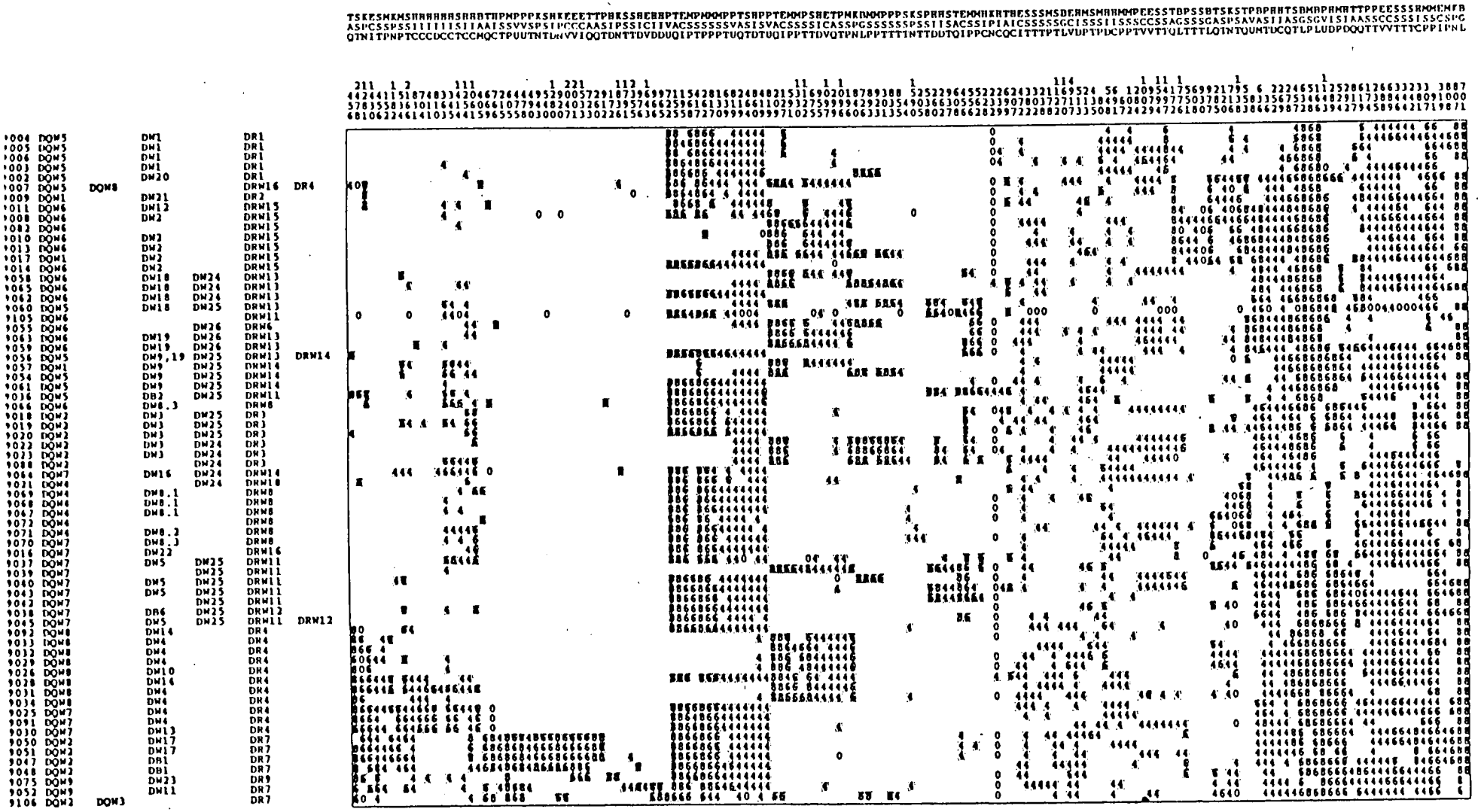
Fig. 33b



Tenth International Histocompatibility Workshop
Class II DRB,DQA,DQB loci RFLP fragments (536). Cells listed by Tree relationships.



Fig. 33c

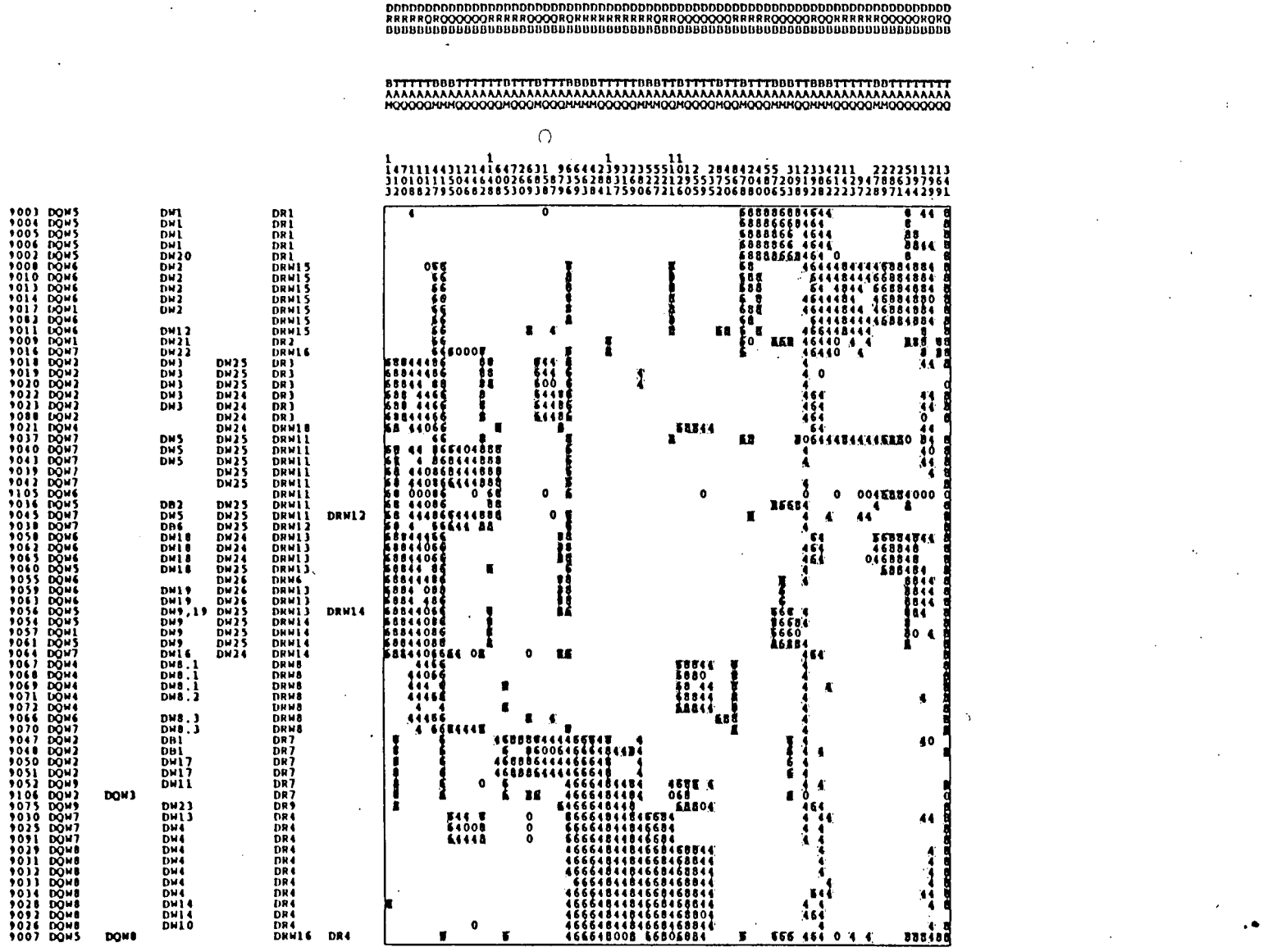


Tenth International Histocompatibility Workshop

Class II DRB,DQA,DQB loci RFLP fragments (536). Cells listed by Tree relationships.



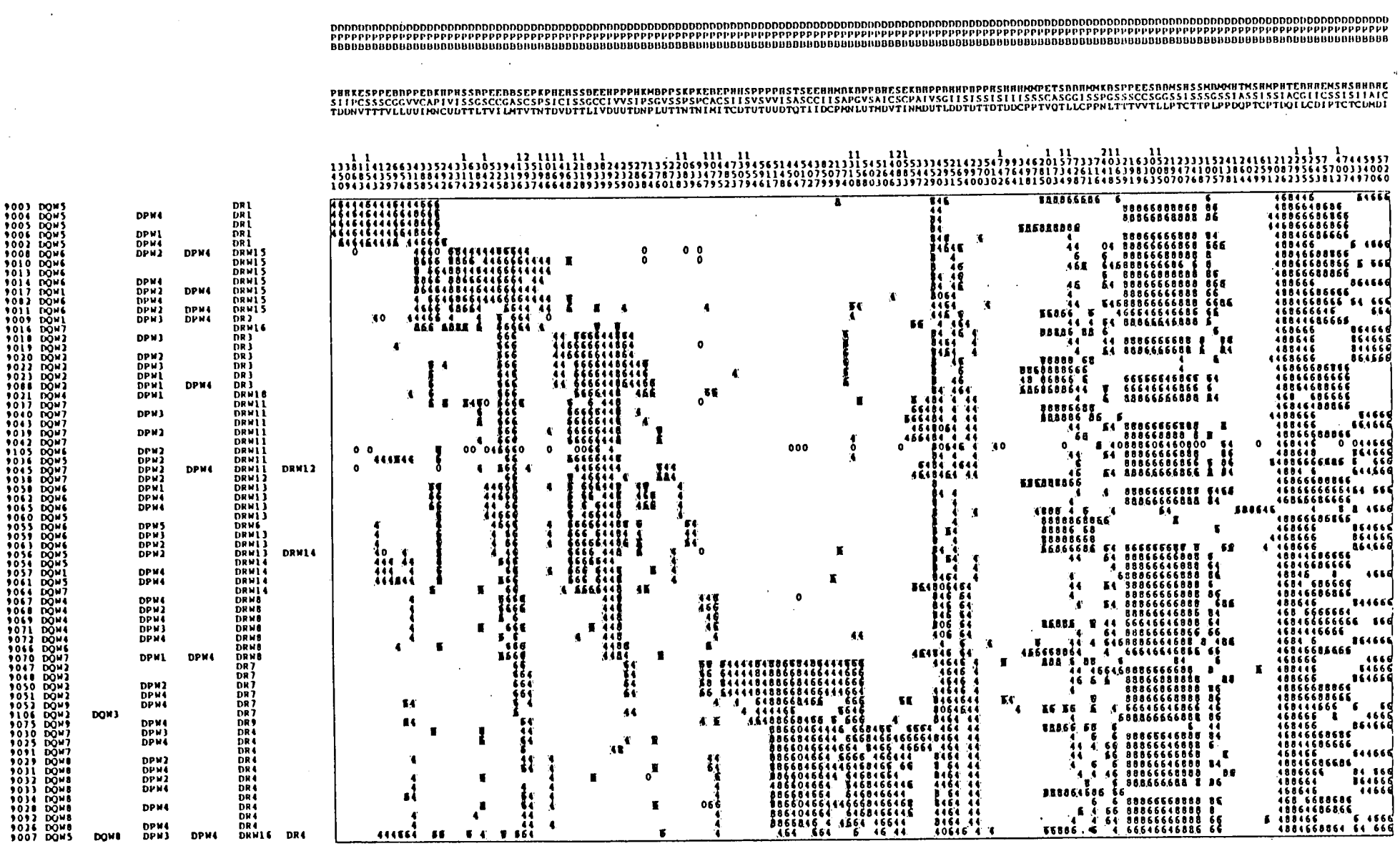
Fig. 33d



Tenth International Histocompatibility Workshop
Class II DRB,DQB RFLP fragments (TAQ,BAM - 72). Positive cluster.



Fig. 34

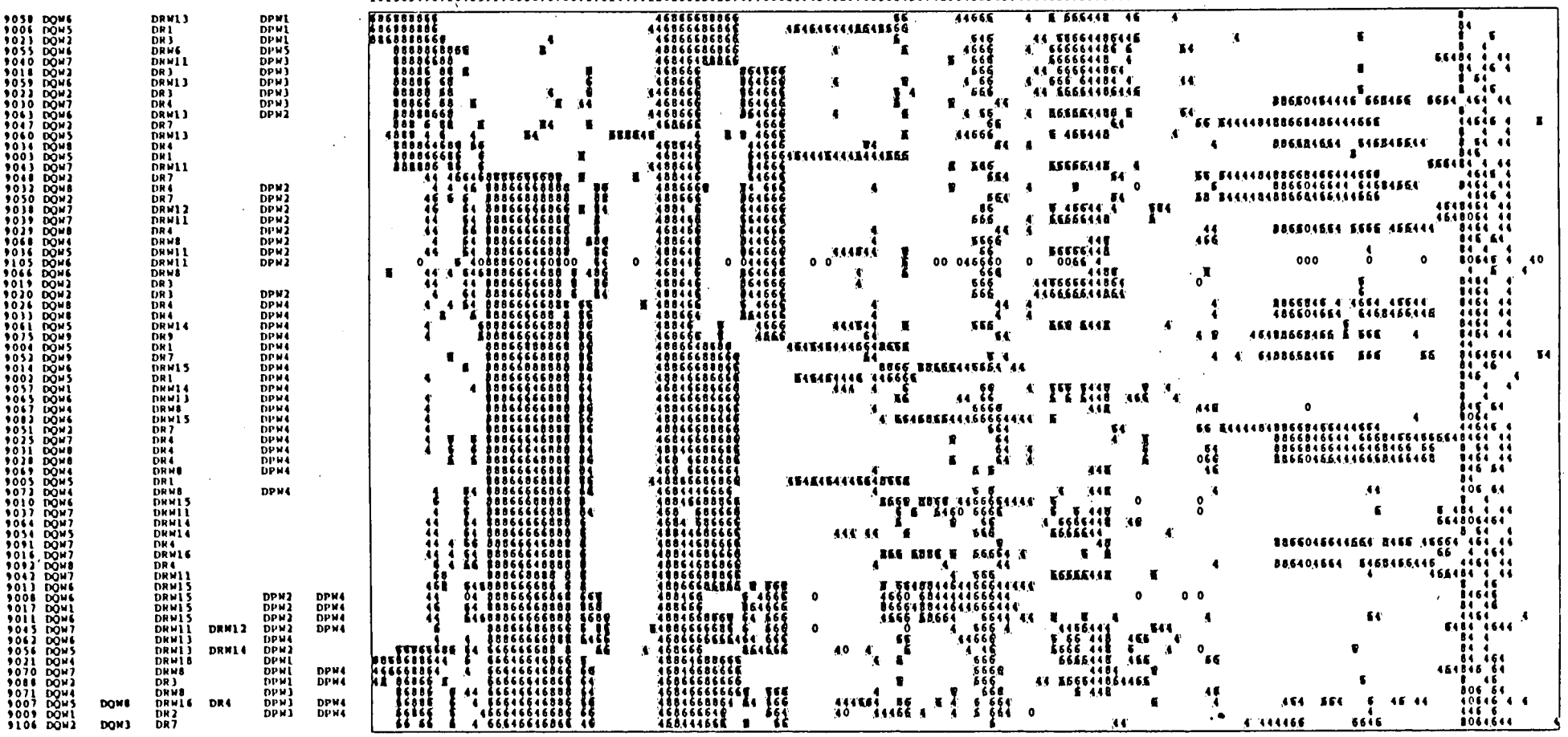


Tenth International Histocompatibility Workshop

Class II DPB locus RFLP fragments (154). Positive cluster. Cells listed by DRw type.



Fig. 35

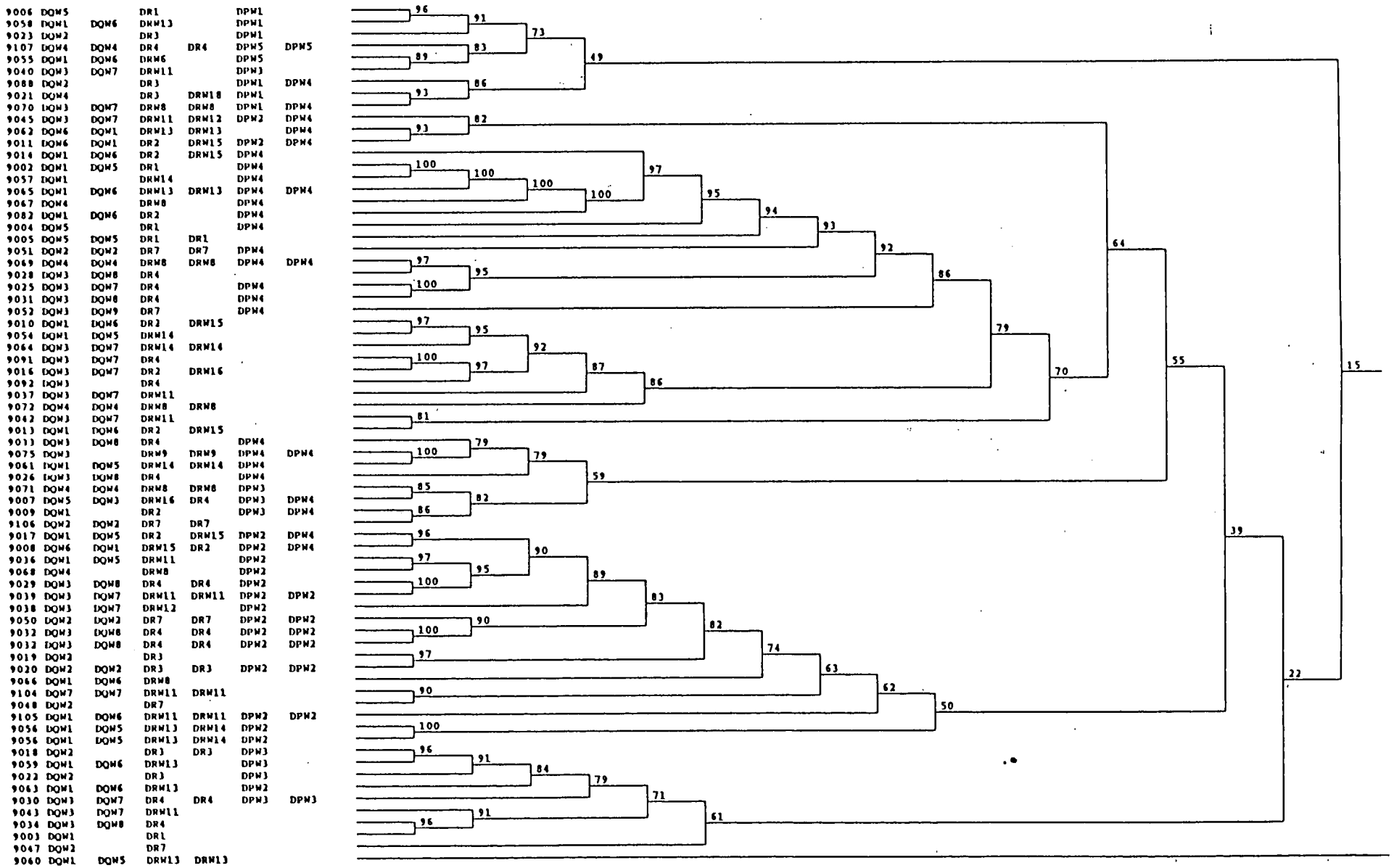


Tenth International Histocompatibility Workshop

Class II DPB locus RFLP fragments (154). Positive cluster. Cells listed by DPw type.

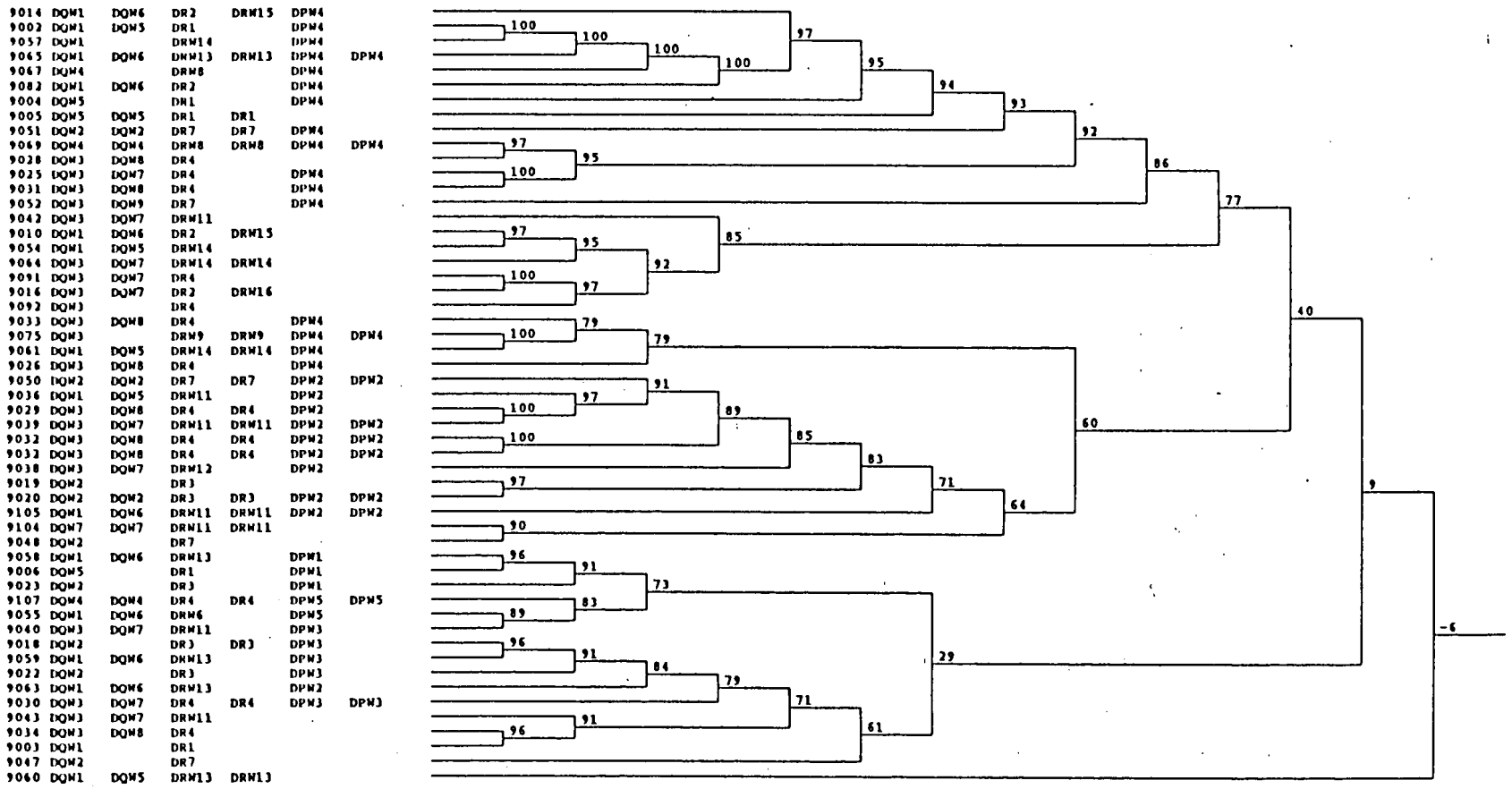


Fig. 36




Tenth International Histocompatibility Workshop
Tree analysis of cell relationships: Class II DPB loci RFLP fragments (57).

Fig. 37



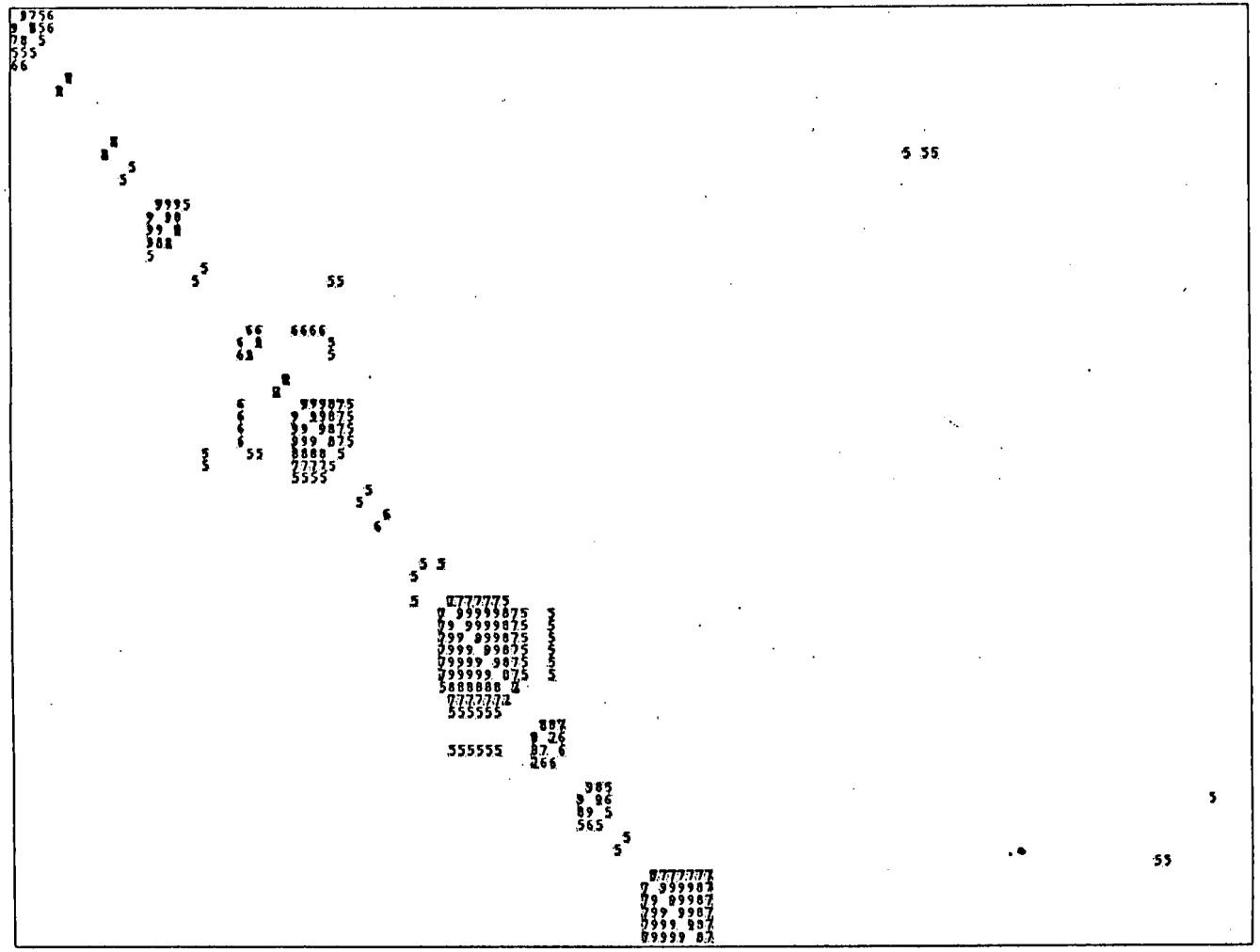

Tenth International Histocompatibility Workshop
W/S cells (53) DPB1,DPB2 loci relationships using Tree analysis.

Fig. 38

Tenth International Histocompatibility Workshop
Class II DPA,DPB loci RFLP selected fragments (98). Positive cluster.



Fig. 39



819 DQA PVU
209 DQA TAQ
127 DQA ECI
591 DQA MSP
278 DQA TAQ
840 DQA KPN
726 DQA BGL
762 DQA PST
2393 DQA BAM
553 DQA TAQ
272 DRA TAQ
198 DRA TAQ
2355 DQA SST
605 DQA MSP
1836 DQA KPN
1312 DQA BGL
325 DQA MSP
231 DQA MSP
250 DQA MSP
761 DPA ECV
1938 DQA SST
1087 DQA BAM
930 DQA SST
285 DQA TAQ
205 DQA SST
1009 DQA BAM
1042 DQA KPN
245 DQA TAQ
389 DRA BGL
660 DQA KPN
465 DQA KPN
492 DQA PVU
1339 DQA ECI
1345 DQA PST
287 DQA MSP
745 DQA HID
1424 DQA KPN
166 DQA BGL
632 DQA BGL
548 DQA MSP
807 DQA KPN
701 DQA BGL
716 DQA KPN
619 DQA TAQ
1286 DPA PVU
323 DPA PVU
658 DPA PVU
1616 DPA SST
445 DPA SST
325 DPA HID
243 DPA PST
473 DPA MSP
415 DPA MSP
314 DPA MSP
223 DPA BGL
417 DPA ECI
1042 DPA SST
867 DPA BAM
750 DPA ECV
1321 DPA TAQ
529 DPA BGL
934 DPA KPN
722 DQA PVU
155 DQA TAQ
195 DQA ECI
568 DQA MSP
838 DQA BGL
684 DQA PST
281 DQA PVU
2478 DQA SST
763 DQA BAM
1176 DQA KPN
483 DQA HID
634 DQA ECI
232 DQA PST

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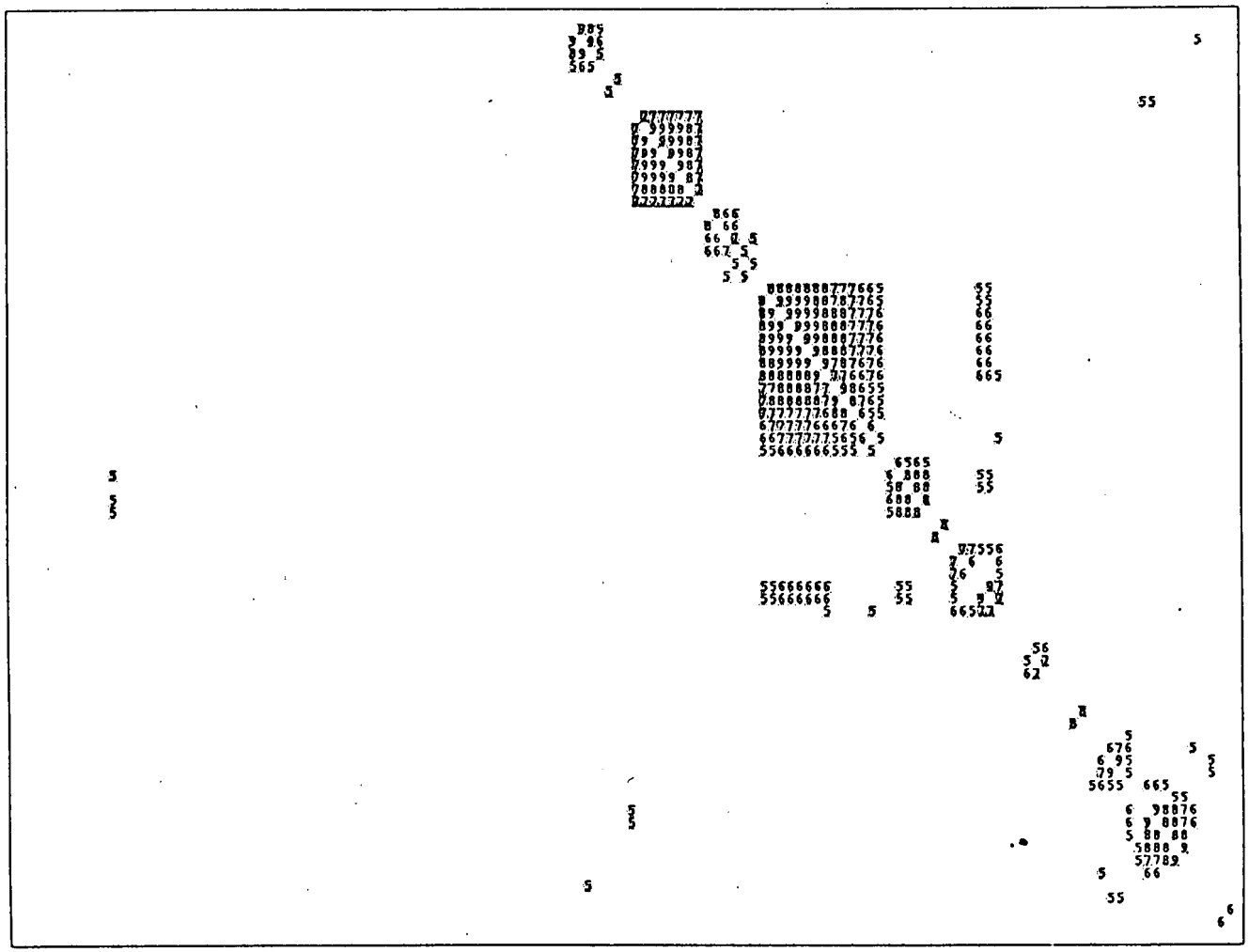
Class II DR,DQ,DX,DP Alpha loci RFLP fragments (136). Fragment cluster.



Fig. 40a



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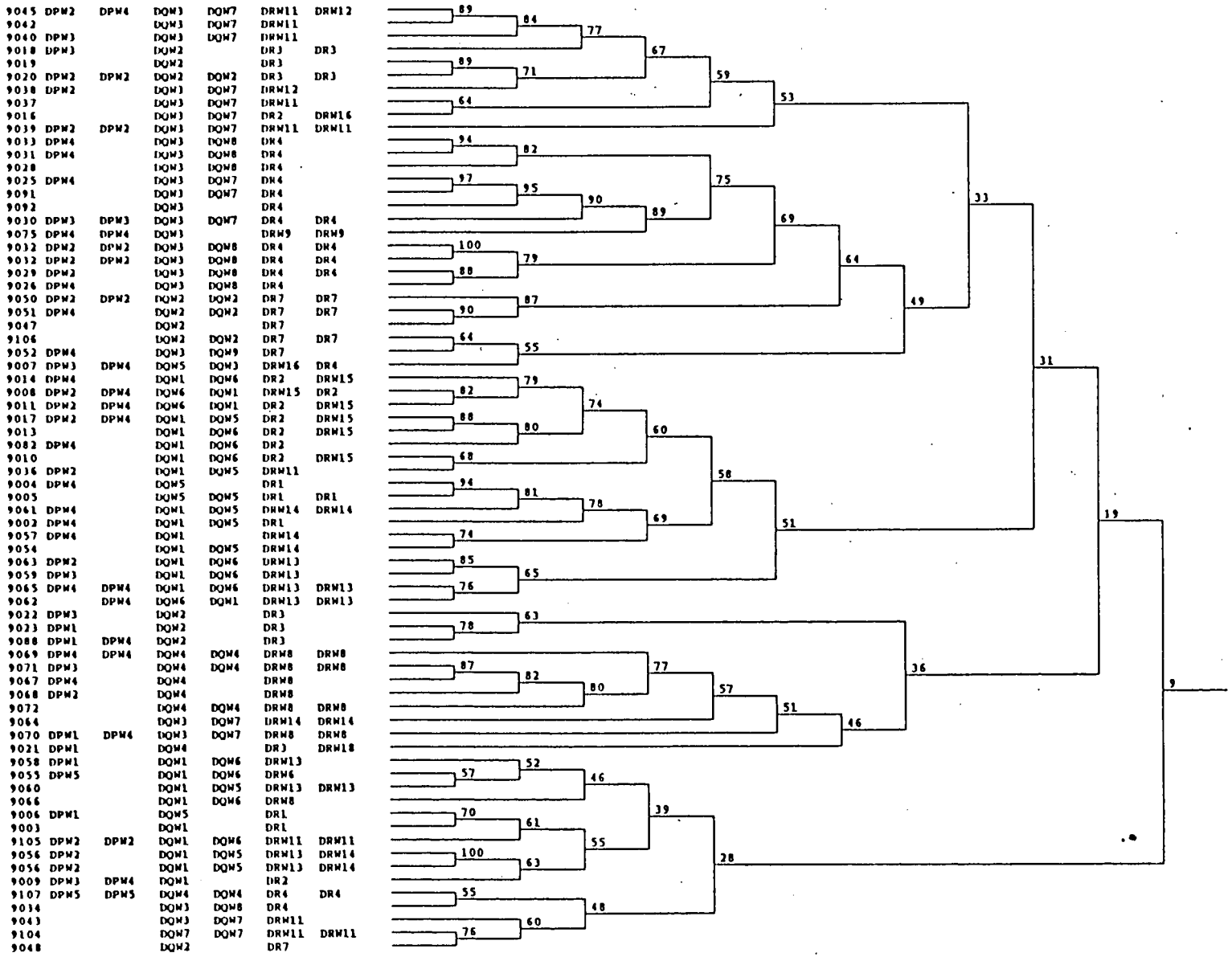
Class II DR,DQ,DX,DP Alpha loci RFLP fragments (136). Fragment cluster.



Fig. 40b

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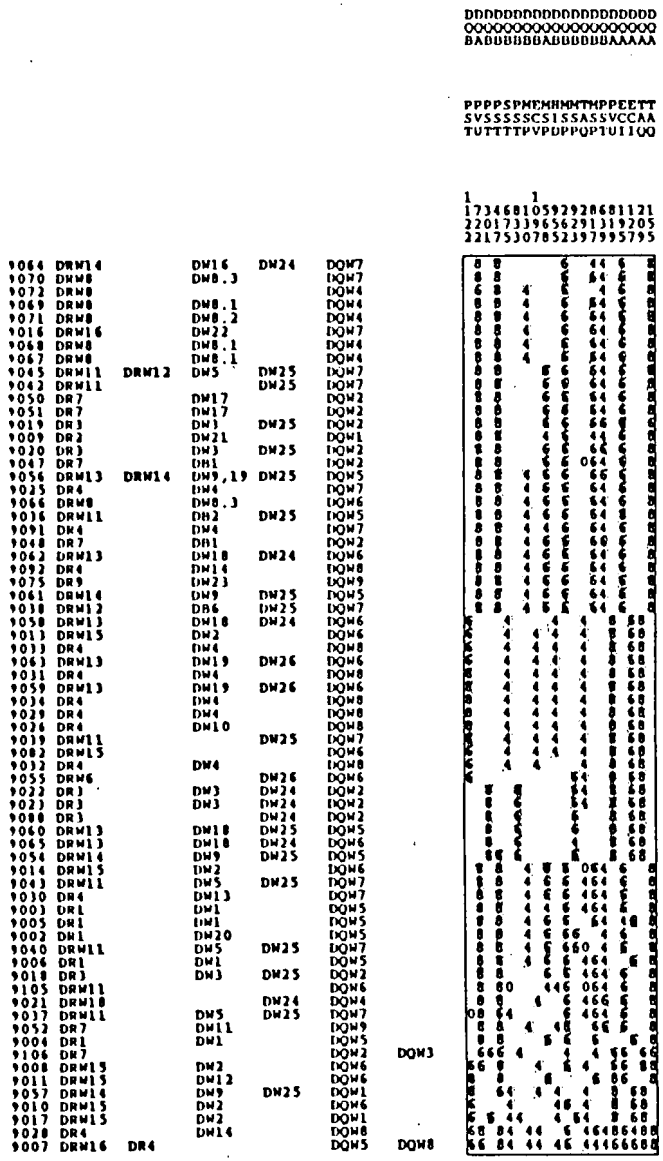
Tree analysis of cell relationships: Class II DR,DQ,DX,DP Alpha loci.

Fig. 41



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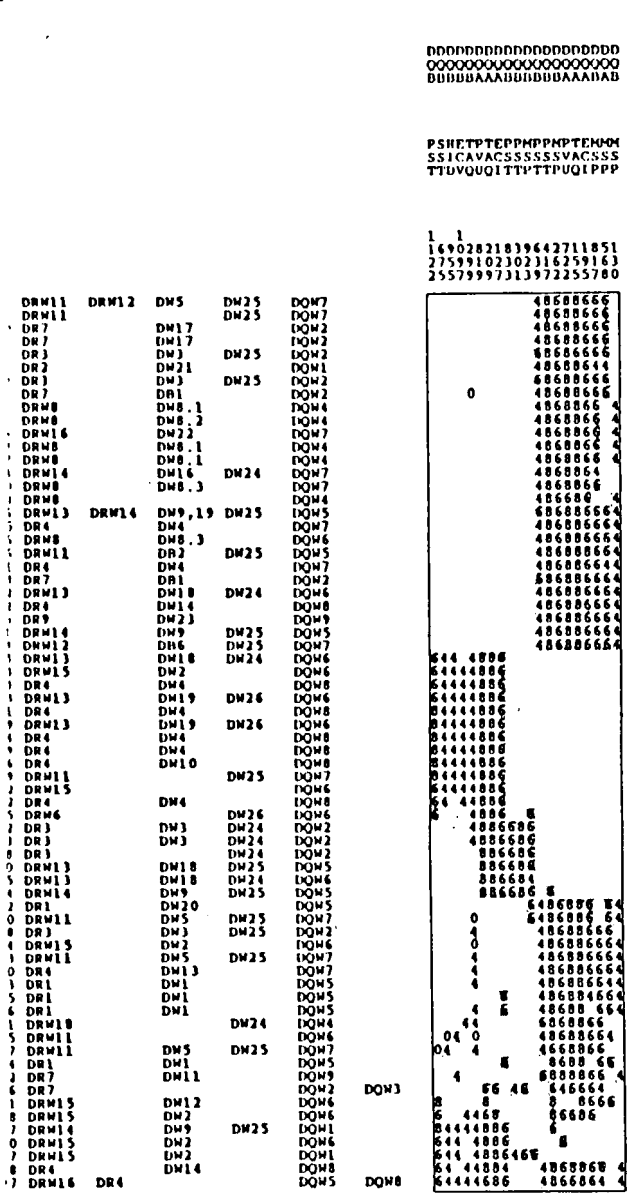
Class II DXA,DQB2 loci RFLP fragments (20). Negative cluster. Cells listed by Tree relationships.



Fig. 42



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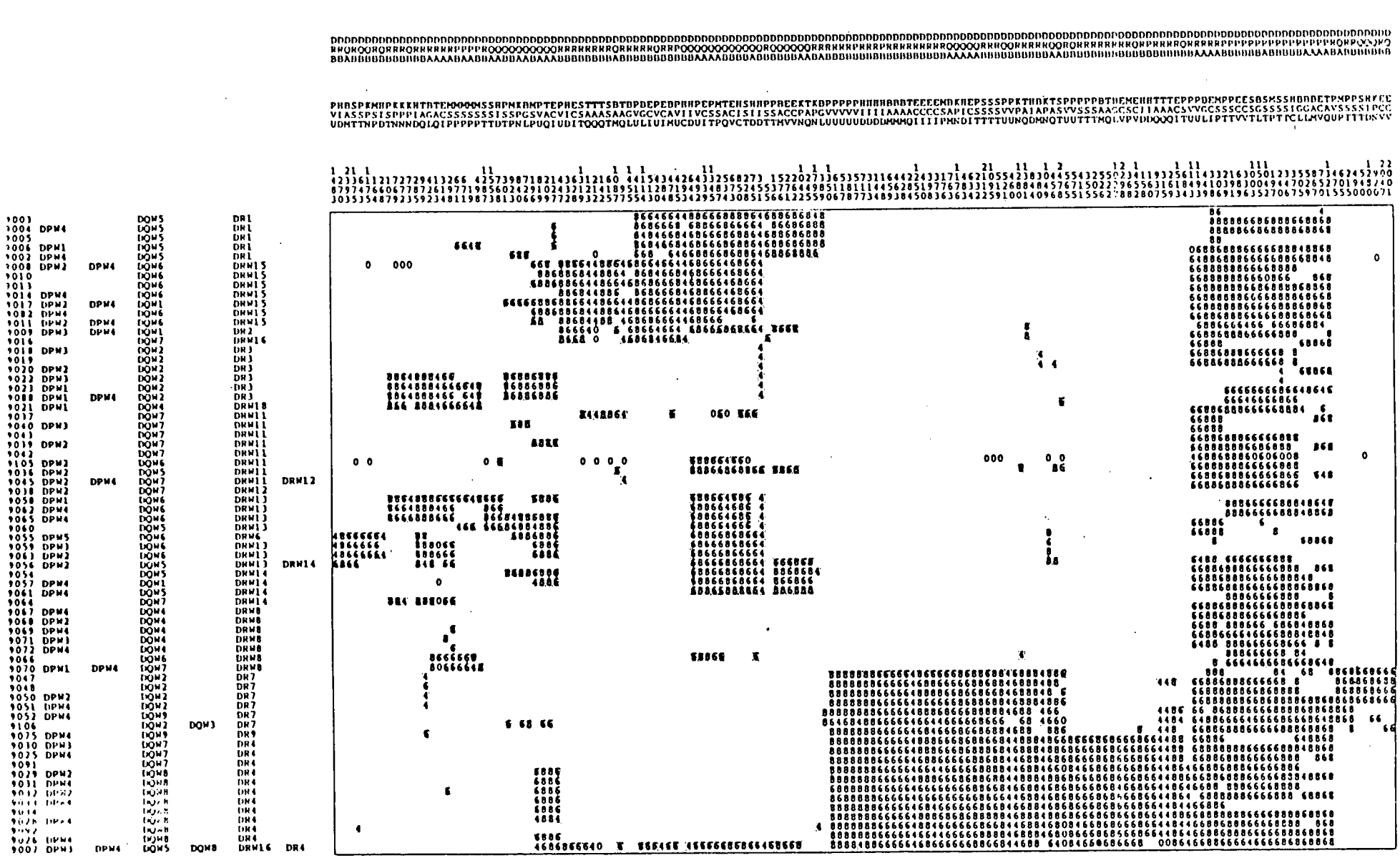
Class II DXA,DQB2 loci RFLP fragments (20). Positive cluster. Cells listed by Tree relationships.



Fig. 43



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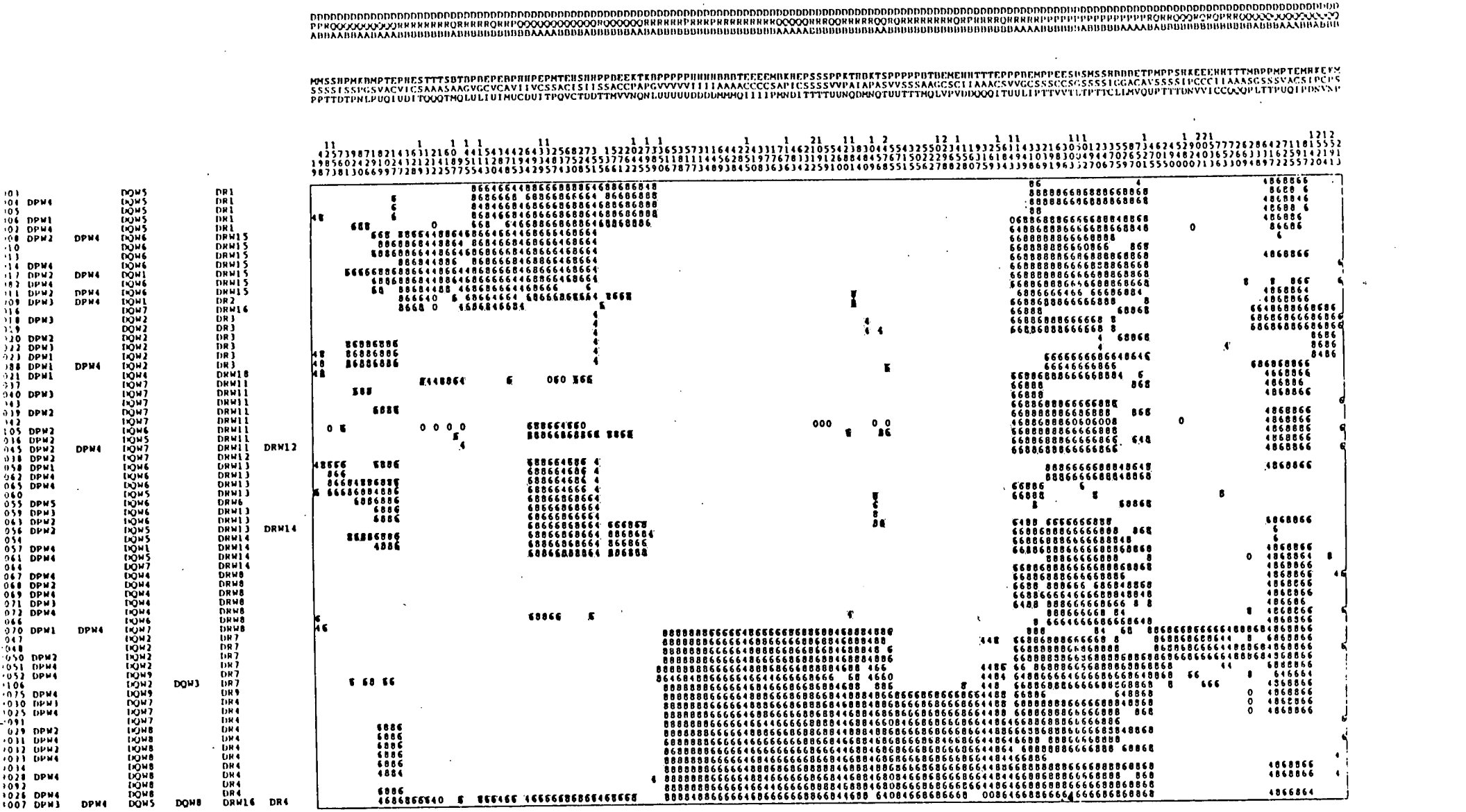
Class II inter-locus co-clustering fragments (175).



Fig. 44a



Tenth International Histocompatibility Workshop
Class II inter-locus co-clustering fragments (175).



Fig. 44b

K

# RFLP - SEQUENCE INTERRELATIONS AT THE DPA AND DPB LOCI

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In the Southern Blot Workshop Summary (1), the RFLP reactivity patterns of 68 Workshop cells were reported. At the DPB1 locus, fragment patterns enabled current DPw1-5 specificities to be distinguished. None of the studied workshop cells were assigned the DPw6 specificity. In addition, RFLP patterns indicative of subtypes of DPw2 and DPw4 specificities were identified, along with patterns associated with DPw 'Blank' cells representing new specificities.

The 68 cells are listed in Fig. 1 according to the current assignment of DPw types based on cellular typing. It can be seen that 19 cells remain unassigned. Of the 49 cells in which there are DPw assignments, 41 bear only one DPw type.

Figure 1 shows the reactivity patterns of 45 fragments detected by the DPA probe, and 53 of the 176 fragments detected using the DPB probe. The total 98 fragments are

arranged to show the patterns associated with the two mutually exclusive fragment clusters for each of the four DP region loci, namely DPB1, DPB2, DPA1 and DPA2. Recognition of locus-related fragments, and of fragment patterns associated with DPw specificities and DP beta chain types, is aided by the use of column (fragment) and row (cell) lines. In the left half of the figure is shown the two clusters of the DPB1 locus, with DPw1, DPw5 and DPw3 occurring in the group that is less frequent among the reference panel cells, and DPw2 and DPw4 occurring within the second, more frequent, group. This division into two main categories is well-known (2).

Fragments present in only one or a few cells, or present in all but one or a few cells, or separate the fragments associated with the DPB1 locus (PST 285 to MSP 107) from the fragments associated with the DPB2 locus (HID 543 to SST 434). These are followed by fragments characterizing the DPA1 locus (MSP 715 to ECI 417). Finally, two fragments (BGL 529, 9th column from end; and BGL 724, last column), and associated fragments (BAM 867 to BGL 724), show a mutually exclusive pattern that is interpreted to represent the DPA2 locus.

In Fig. 1, the 8 cells at the bottom of the list (9056, 9021, 9070, 9088, 9071, 9007, 9009, 9106) are heterozygous for the two main clusters associated with the DPB1 locus. Cells 9071 and 9007 are also seen to be heterozygous at the DPB2 locus,

while cells 9009 and 9106 have incomplete patterns for the two DPB2 clusters. Four additional cells (9013, 9011, 9045, 9062) are also heterozygous only at DPB2. Patterns of heterozygosity are more readily discernable in Fig. 2 in which negative clusters of loci-defining fragments have been rearranged into DPB and DPA locus groups. The 6 cells heterozygous only at DPB1 and not at DPB2 (9056, 9021, 9070, 9088, 9009, 9106), are also heterozygous at the DPA1 locus. That the two DPA mutually exclusive BGL fragments (BGL 724, BGL 529) do correspond to a DPA locus distinct from DPA1 is supported by the heterozygosity pattern involving cells 9008, 9017, 9011, 9062, 9070, 9088, 9071, and 9009. The 6 cells which are heterozygous either for DPB2 and/or DPA2, but not DPB1 and/or DPBA1 (9013, 9008, 9017, 9011, 9045, 9062) include 4 that are assigned as DPw2/w4 series heterozygotes (9008, 9017, 9011, 9045). In the Tree dendogram (Fig. 4), 9017 and 9008 are seen to be closely related, as are 9045 and 9011, along with 9062 and 9013. These four are seen in the Tree dendogram (Fig. 4) to have close relationships, along with 9013 and 9062. Cell 9062, and possibly also 9013, may be heterozygous for two alleles of the DPw2/w4 series.

Sequence analysis of the DP beta second exon encoding the outer domain has revealed 14 sequences at the DPB1 locus, and 2 sequences at the DPA1 locus (3). These sequences are shown in Fig. 3, along with one DPA2 locus sequence (called SXA in

Fig. 3), and one DPB2 sequence (SXB). The two alleles of the DPA1 locus have been called DPA1 and DPA2.

The first main contribution of sequence analysis has been to distinguish subtypes of DPw2 and DPw4. The listed DPw4 specificities are encoded by the DP beta 4.1 sequence, for all but one cell (No. 9072), which is DPB4.2. Cells cellularly typed as DPw2 are all of the DPB2.1 sequence subtype, again with one exception (No. 9020, which is DPB2.2). Among the reference panel cells, DPw typing has predominantly identified the DPB2.1 and DPB4.1 sequence alleles of the DPB1 locus. Furthermore, sequence analysis of DPB1 alleles has revealed that 11 of the 19 cells lacking a DPw assignment are either DPB2.2 or DPB4.2 (Nos. 9019, 9066, 9010, 9054, 9064, 9091, 9016, 9092, 9037, 9042, 9013). Apart from cell 9013, which is heterozygous at DPB2, all 11 cells appear to be homozygous at both DPB1 and DPB2 loci. Cell 9034 has been sequence typed as DPB4.2, DPB10. However, RFLP analysis reveals no evidence of heterozygosity for this cell, nor of a fragment pattern consistent with the DPw4/DPB4.2 type. The only fragments present are those associated with the DPB New allele cells 9043 and 9003, with which cell 9034 forms a separate subcluster within the DPw1/w5/w3 group. This discrepancy aside, all but one (cell 9048) of the cells associated with the DPw2/w4 cluster DPw Blank have DPB2.2 or DPB4.2 allele sequence types.

The second main contribution of DPB1 second exon sequence analysis has been the identification of new alleles associated with the DPw1/w5/w3 group. Among the reference panel cells, the DPB1 sequence-defined allele DPB10 (9034) and four of the new RFLP patterns (Cell nos. 9060, 9047, 9003, 9043), associate with the DPw1/w5/w3 group. Cell nos. 9056 and 9106 are heterozygous, having New specificities associated with the DPw1/w5/w3 group on one haplotype, and alleles of the DPw2/w4 group on the other. Based on beta chain sequencing, cell 9106 has DPB4.1. Cell 9056 has been PLT typed as DPw2.

Two additional cells (Nos. 9104 and 9107) were not serologically typed and therefore were not included among the 68 reference panel cells tested both by serology and RFLP. RFLP data on these two cells were included in the cluster analyses from which the Tree dendograms were generated. In Fig. 4, Tree analysis utilizing 98 fragments selected for association with DPA1, DPA2, DPB1, and DPB2 loci has been applied to all 70 cells. In Fig. 5, Tree analysis utilized cells that were homozygous at the two DPA and two DPB loci. Cell 9107 has the DPB1 sequence allele DPB5 characteristic of DPW5 cells. The RFLP fragment pattern of cell 9107 is, in fact, most similar to that of the DPw5 cell 9055, as demonstrated in the Tree dendogram (Fig. 4), but there is a significant pattern difference between the two. The Similarity Index between 9107 and 9055 is 75, an association

of appreciably lower strength then exists for many other cell pairs. From RFLP analysis, it is unlikely that both cells are homozygous for the same DPw5 allele. However, it must be recognized that differences at non-expressed loci contribute to a low Similarity Index even where homozygosity exists for exon encoded alleles.

From the Tree dendogram it can be seen that all the cells having DPB1 New specificities, except 9048, are associated with the DPw1/w5/w3 cluster. These cells are numbers 9043, 9034, 9003, 9104, 9066 and 9060. Cells of the DPw1/w5/w3 cluster have been subclustered into those having DPw1/w5 and those with DPw3. In Fig. 4, these two subclusters are separated by 5 cells (9088, 9070, 9009, 9106, and 9021), the first three of which were determined to be DPw1 or Dpw3/DPw4 heterozygote. Cells 9106 and 9021 are heterozygous at DPA1 and DPB1 loci, and are presumptive DPw heterozygotes. Of the DPB New cells, 9047 is included within the DPw3 subcluster, while the remainder are associated with the DPw1/w5 subcluster. Their cell relationships, based on differences associated with pattern variation involving DPB fragments MSP 197, SST 240, MSP 107, SST 1365, SST 318, MSP 213, and BGL 728, among others, can be examined in Figs. 4 and 5. Most obviously, the DPB New specificity represented by cell 9060 is associated with unique fragments, and a unique pattern of

fragment absence, distinguishing it from all other cells. It is positioned at the bottom of both Tree dendograms. The next, least dissimilar, cell is that of 9066, but the Similarity Index between the two is very low. New DP specificity cells 9003 and 9034 pair together. Cell 9043 has the next highest Similarity Index to this pair. These three cells form a separate subcluster. Tree analysis also indicates that cell 9063 appears to have been mistyped as DPw2, since it DPw3 subcluster-associated, and has no fragment pattern characteristics of DPw2. Cell 9104 has been sequence typed as DPB9, DPB New heterozygous at DPB1 locus.

The RFLP fragment patterns of cell 9104 (DPB9, DPB New) and cell 9048 (DPB12) are very similar (Figs. 4, 5 - Similarity Index 86). They form a DPw2-associated cluster along with cells 9105 and 9056. This is also seen in the fragment cluster patterns (Figs. 1, 2) which indicate an association of 9048 and 9105 with the DPw2/w4 cluster, although comparison of the fragment pattern similarity between these two cells has to take account of the doubtful fragments (scored as '0') associates with cell 9105. Cell 9056 is clearly heterozygous at both DPB1 and DPA1 loci. As mentioned previously, the non-DPw2-associated haplotype in cell 9056 is a DPB New allele of the DPw1/w5/w3 cluster. Cell 9048 lacks the fragment SST 346 which is a characteristic of the DPB1 sequence subgroup, DPB2.2 (cell nos. 9019, 9020 and 9066). There is no close

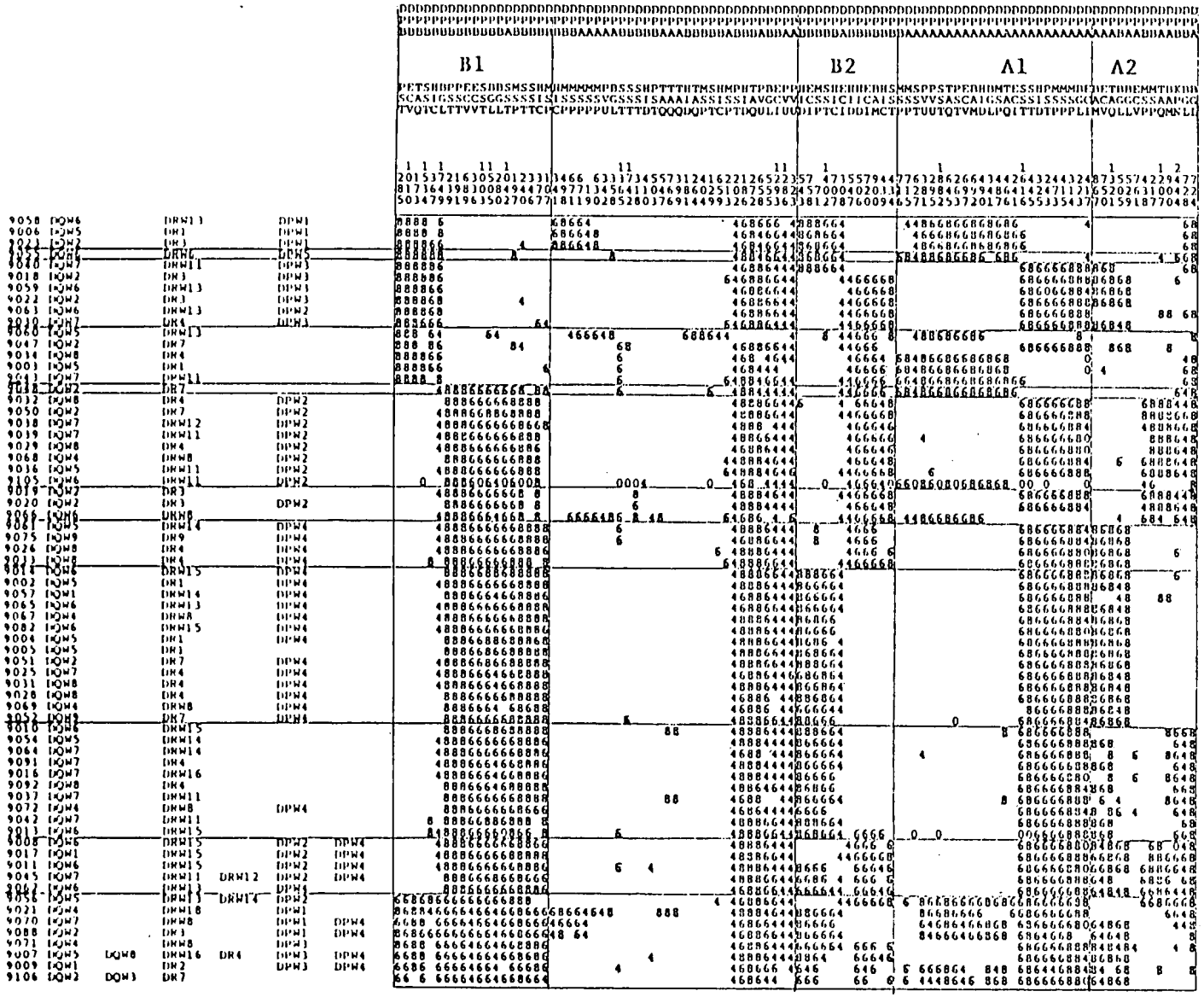
relation at a sequence level between DPB12 and either DPB4.2 or DPB2.2 (Fig. 3). The alignment is, in fact, closer to the DPB sequences of DPw1/w5/w3 series alleles. This illustrates why caution should be exercised when comparing new specificities and currently known types based on sequence and RFLP fragment pattern similarities until more information enables any generalizations to be discerned. The best association might be expected when restriction endonucleases are employed which have intra-exonic restriction sites. Although restriction sites for enzymes used in the workshop exist in the second exon, size considerations indicate that they are unlikely to have contributed to the observed RFLP fragment patterns. For the present, it should be recognized that RFLP patterns only indirectly reveal allelic differences by linkage disequilibrial-based associations between sequences bearing restriction sites, on the one hand, and allele-distinguishing exon sequences, on the other.

The objective of HLA typing by RFLP is to distinguish between haplotypes bearing different allelic specificities. This requires the selection of enzymes which generate fragments that exhibit linkage disequilibrium with sequence variants. In addition to the selection of informative enzymes, HLA DPB type distinction is assisted by utilizing the contribution of the DPB2 and DPA2 loci. Fragment patters at these non-expressed loci stratify haplotypes into different DPB sequence

types. For example, the DPA2 fragment BGL 724 distinguishes between DPw4.1 and 4.2 cells. Reciprocally, the mutually exclusive DPA2 fragment BGL 529 is present only in DPw4.1 cells, and not in either DPw4.2 or DPw2 cells. The four DPW4.1 cells (Nos. 9061, 9075, 9026, 9033) are distinguishable from the remaining DPw4.1 cells on the basis of DPB2 type. It remains to be determined whether this stratification of DPw4.1 cells reflects unrecognized exon sequence differences. Similarly, for the DPw1/w5/w3 cluster, DPA1 typing enables DPw1 and DPw5 to be distinguished from DPw3. Detailed examination of Fig. 1, in conjunction with cell relationships seen in Figs. 4 and 5, reveal other examples where multi-locus haplotype stratification enables allelic specificity assignment.

In conclusion, utilizing DPB and DPA locus probes, there are RFLP patterns for the five DPw specificities DPw1-w5, and for the corresponding DPB1 sequences represented among the reference panel cells. RFLP patterns have also been identified for the additional DPB1 sequence types (DPB2.2, DPB4.2, DPB9, DPB10 and DPB12), and for the DPB New specificities for which sequence information is not yet available. Tree analysis provides a useful indication of the similarity between haplotypes bearing these new specificities. In addition to the DPB types whose sequence is shown in Fig. 3, and the DPB New specificities indicated by the RFLP

patterns, unpublished results of Caucasian and Chinese cells reveal at least twelve additional DPB1 sequences. Thus, polymorphism at the DPB1 locus appears to involve at least 24 DPB1 sequence variants.

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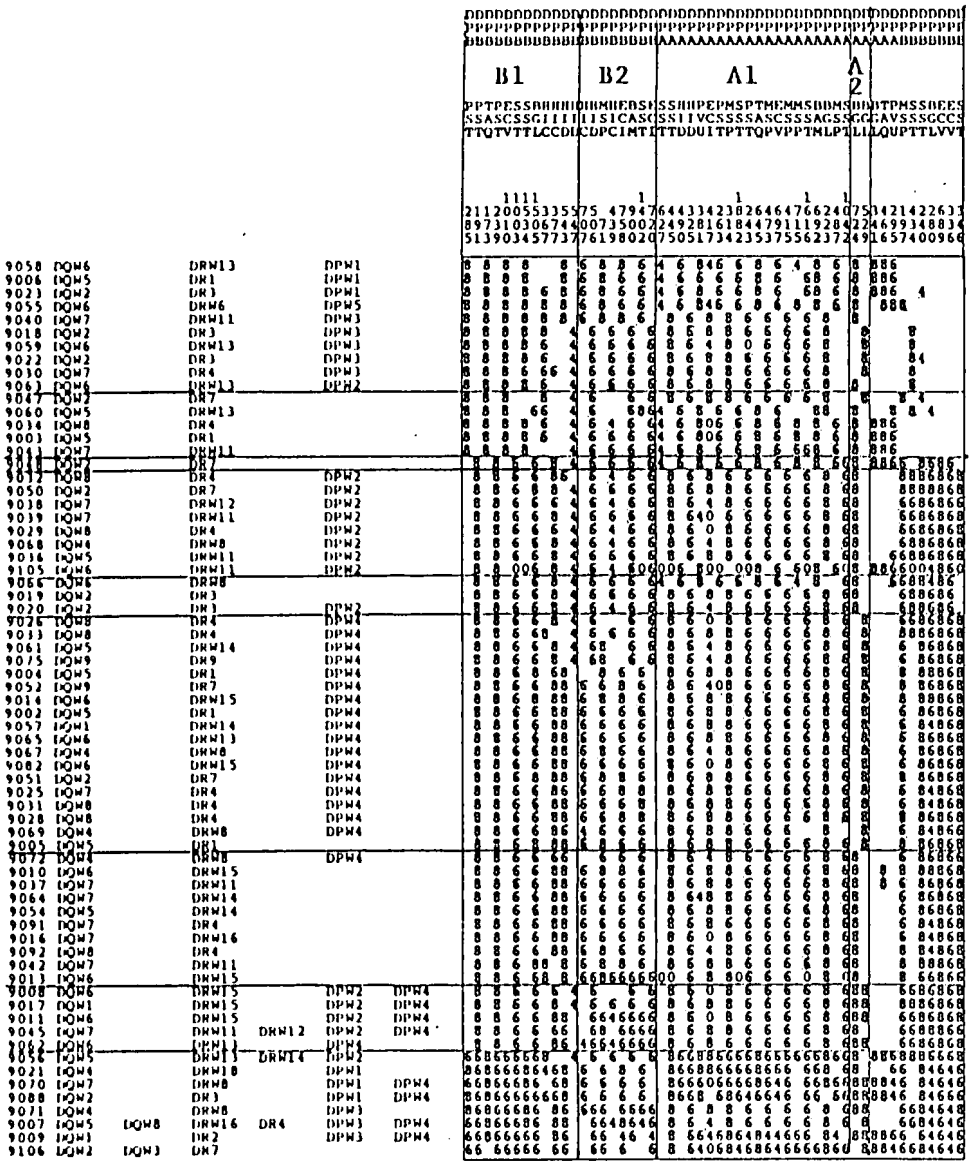
Class II DPA,DPB loci RFLP selected fragments (98). Positive cluster.



Fig. 1

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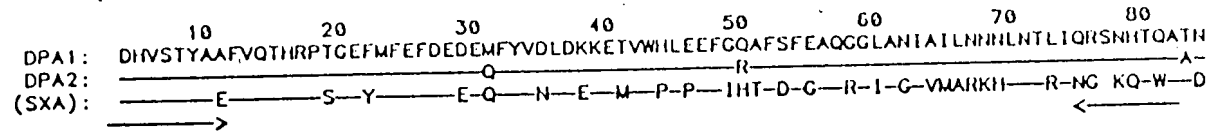
Class II DPA,DPB loci-identifying RFLP fragments (52). Negative cluster.



Fig. 2

A. DP-alpha




B. DP-beta

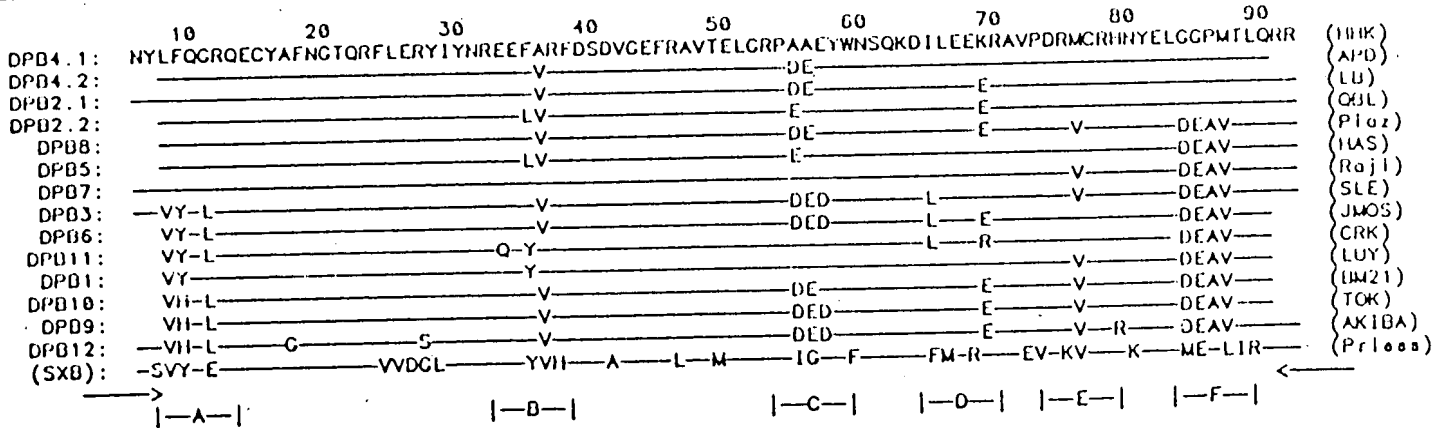
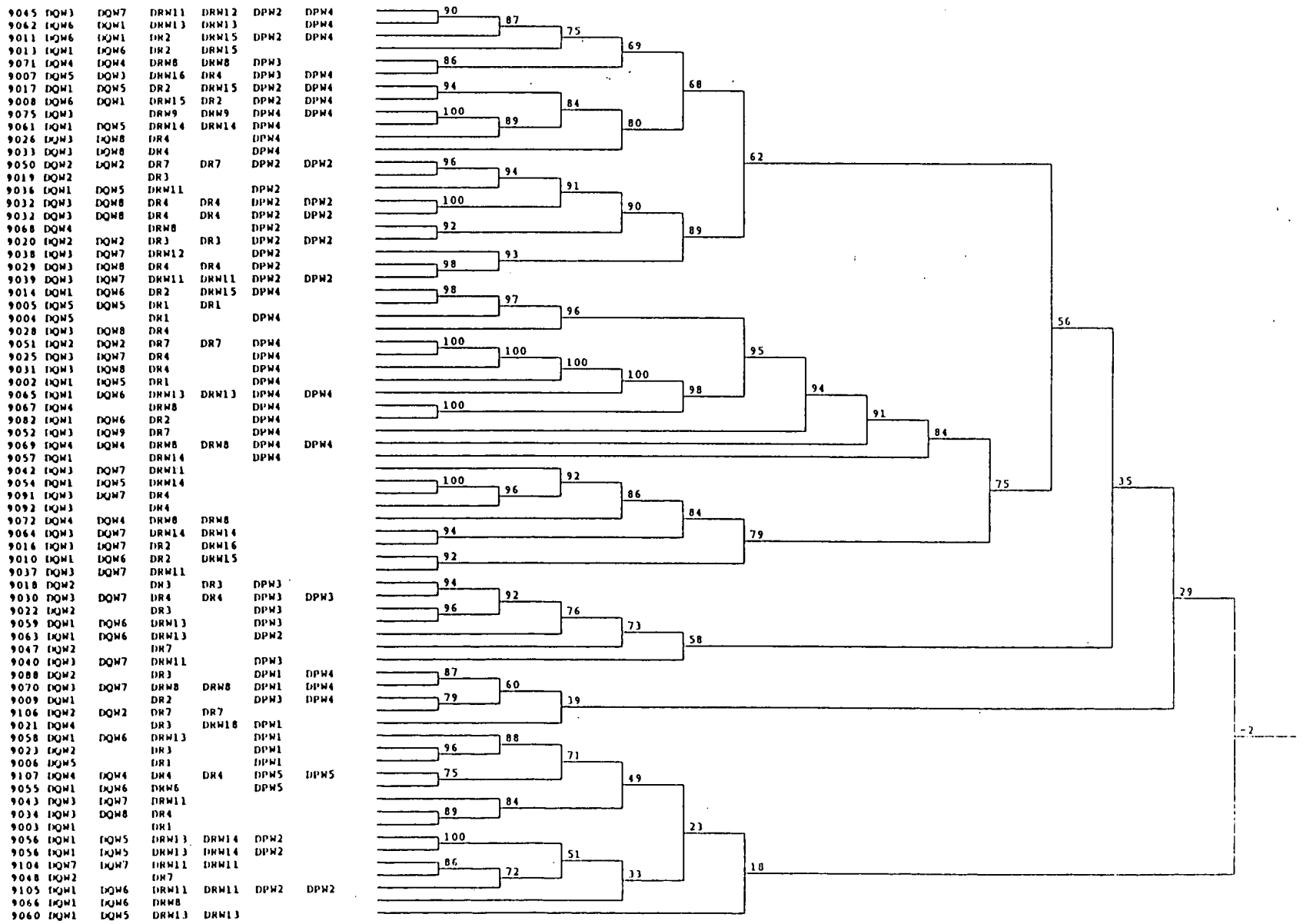



Figure 3. Alignment of the Protein Sequences of the HLA-DP Genes. The nucleotide sequences in figure C were translated into the standard one-letter amino acid code and aligned to the DPB4.1 allele. As before, a dash indicates identity with the prototype and a space indicates the sequence was not determined. The positions are for the mature peptide subunits, and the arrows indicate the positions of the PCR amplification primers. The designations of the alleles are shown at left, and representative sources indicated at the right.

A: HLA DP-alpha alleles. The sequences of the two published DP-alpha alleles are shown. For comparison, the sequence of the DP-alpha pseudogene, SX-alpha, is also included.

B: HLA DP-beta alleles. The sequence of the DP-beta pseudogene, designated SX-beta, is also included.

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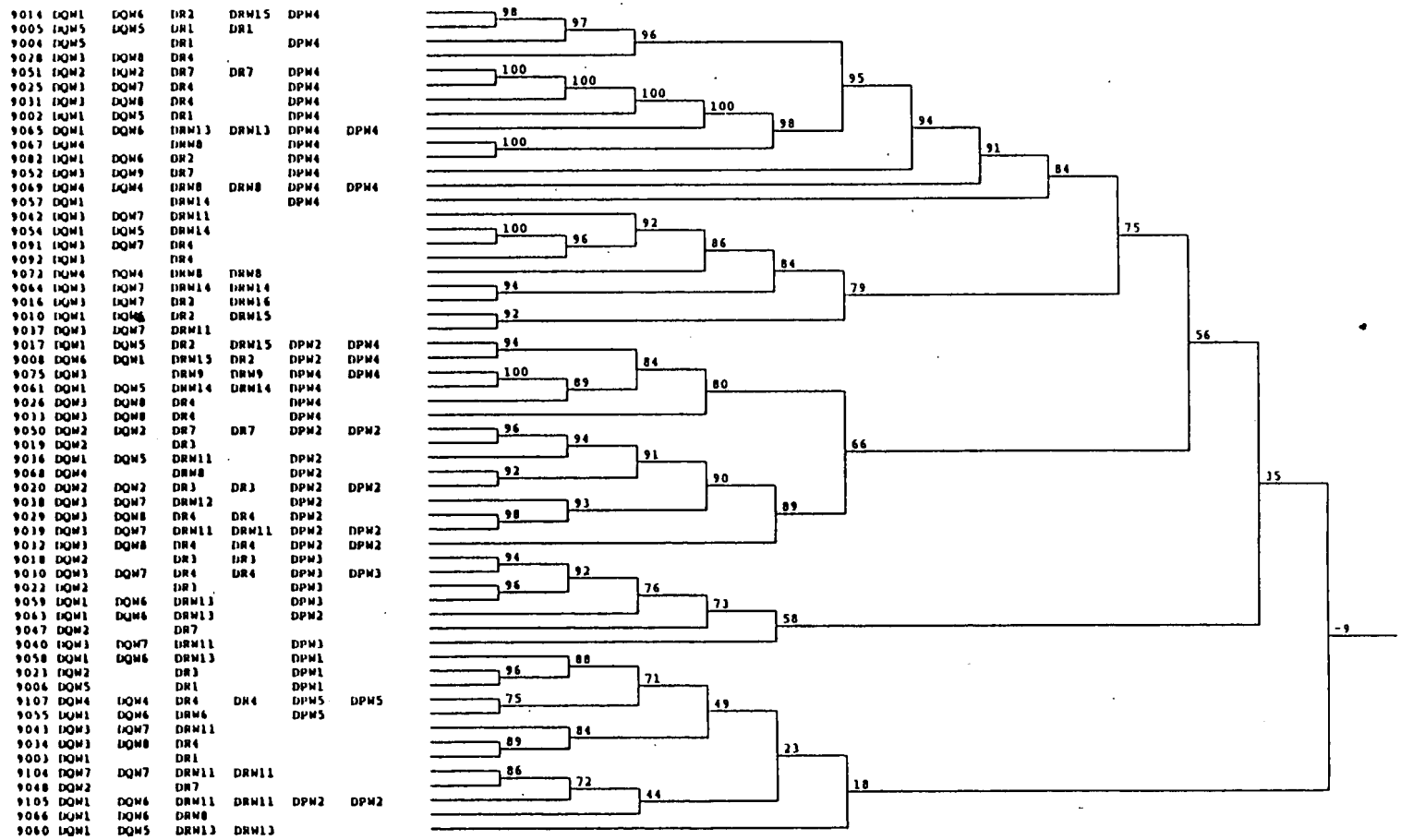
Tree analysis of cell relationships: DPA,DPB loci RFLP selected fragments (45 + 53: total 98).

Fig. 4

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Tree analysis of cell relationships: LPA,DPB loci RFLP selected fragments (98). DP homozygous cells